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PHYSIOLOGIC STUDIES ON THE STOMACH OF A WOMAN WITH A GASTRIC FISTULA

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THE CHAIN of circumstances which permits direct observation and study of the interior of the human stomach is rare. In the entire record of medical history it has occurred but four times: (1) in Beaumont's classic study of Alexis St. Martin, first published in 1833,[1] (2) in Richet's study of a patient in 1878,[2] (3) in Carlson's study of Mr. V. in 1912[3] and (4) in Wolf and Wolff's study of Tom in 1940[4]. Each of these was made on a male patient.

When the opportunity presented itself to study a patient who had undergone a gastrostomy, we considered it to be of value to add further observations to those which have been made, particularly since our patient was a young woman. The possibility that physiologic activity in the stomach of the female may differ from that observed in the male was suggested by the strikingly greater incidence of duodenal and gastric ulcer (a 4 to 1 ratio) reported for males.

REPORT OF A CASE

History.—On the night of Dec. 15, 1944, Doris B., a 21 year old Negro woman, while home for the Christmas vacation from college went to the medicine cabinet in the kitchen of her home to obtain some powders which she had been

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1. Beaumont, W.: Experiments and Observations on the Gastric Juice and the Physiology of Digestion, Plattsburgh, F. P. Allen, 1833, pp. 1-260.

2. Richet, C.: Du sac gastrique chez l'homme et les animaux, ses proprietes chimiques et physiologiques: Appendice A.: Tour de l'anatomie et de la physiologie, Paris, Germer-Bailliere & Cie, 1878, vol. 14, p. 170.

3. Carlson, A. J.: Contributions to the Physiology of the Stomach: I., Am. J. Physiol. **31**:151-168, 1912.

4. Wolf, S., and Wolff, G.: Human Gastric Function, New York, Oxford University Press, 1943, pp. 1-185.

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in the habit of taking for dysmenorrhea. These consisted of a teaspoon of powder with several crushed acetylsalicylic acid tablets. Because of confusion in the placing of bottles in the medicine cabinet, she inadvertently took lye. She immediately complained of burning in the mouth, but this was soon replaced by a sensation of generalized pain which was constant in character and later was associated with vomiting.

The patient entered the Homer G. Phillips Hospital on Dec. 16, 1944, but on the request of her mother she was sent to St. Mary's Hospital, where emergency treatment was carried out and where she remained for sixteen days. Dysphagia constantly increased during this time. On Jan. 15, 1945, the patient was again admitted to the Homer G. Phillips Hospital, and five days later a gastrostomy was performed under spinal anesthesia. At that time a string was passed through the esophagus and dilation was carried out. However, the patient remained unable to swallow. Moreover, it was necessary to perform another gastrostomy on March 26 because of stenosis of the original opening. After this operation, the wound became infected and broke down, which resulted eventually in a large opening

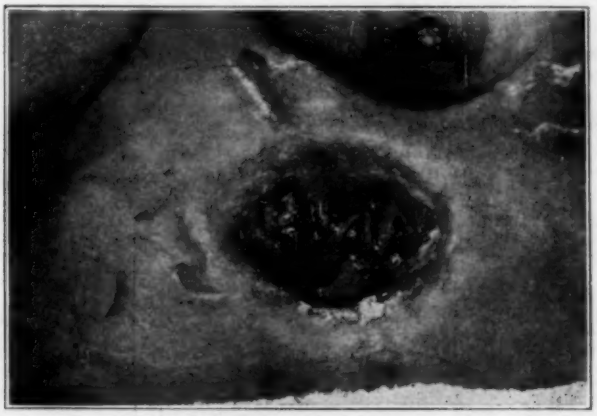

Fig. 1.—The cannula has been removed from the gastrostomy opening, with the patient in the erect position. The herniated mucosa is the posterior wall of the stomach and is the area where color changes were observed.

approximately 6 cm. in diameter lateral to the left rectus muscle. It was so large that feedings and gastric secretions were not retained but escaped; this led to excoriation of the skin. The patient lost considerable weight, and a specially designed soft rubber cannula was finally inserted in the gastrostomy opening to prevent leakage of gastric juice. A high protein liquid diet was given through the opening, and normal weight was soon regained.

Removal of the cannula revealed herniation of a considerable area of the posterior wall of the stomach through the gastrostomy opening, with increase in the intra-abdominal pressure (fig. 1). The gastrostomy opening was located along the anterior portion of the greater curvature of the stomach approximately 6 inches (15 cm.) from the pylorus and 7 inches (18 cm.) from the cardia. The external opening was lateral to the umbilicus and approximately in the mammary line. When the patient lay on her left side, the stomach emptied itself of its fluid content fairly well. The fluids can be easily collected in any glass vessel with a slight flare to the upper rim.

The size of the opening in our patient was 6 by 8 cm. Beaumont's Alexis St. Martin had an opening 6 cm. in circumference approximately 7 cm. to the left of the cardia near the left superior termination of the greater curvature.[1] Carlson's Mr. V. had an opening on the lesser curvature about 8 cm. above the umbilicus and a little to the left of the median line. The fistula was only large enough to admit a rubber tube 1 cm. in diameter, which was always kept in place[3]. Wolf and Wolff's Tom had a defect in the abdominal wall 3.5 cm. in diameter through which a collar of gastric mucosa herniated[4].

The patient's personal history was not particularly unusual. Two brothers, the father, the mother and the stepfather are all living and well. Her menstrual history was not unusual except for moderate dysmenorrhea and slight menstrual irregularity during the early stages of her illness. Her friendships, likes and dislikes seem to have followed a usual pattern.

The patient had attended public school and high school and had been a year and a half at college. Her desire was to be a physical education teacher in an elementary school. Her scholastic standing was consistently above average, and she was the school's ping-pong champion. She stated that most of her desires and wants have been fulfilled without difficulty. On the basis of this history and after a rather long evaluation of her condition in Barnes Hospital, to which she had been transferred for further care, there was little evidence to substantiate any belief that the swallowing of the lye was other than accidental or that there was any intent to commit suicide.

Since it was believed that the patient presented such an excellent opportunity for physiologic study, she was approached with the request that she permit us to make observations on her stomach while she was undergoing other treatment. To this she readily assented with a definite show of enthusiasm at being able to perform something beneficial. These negotiations were carried out in a frank manner, with full explanations as to what was desired and what was planned and with the proviso, of course, that the plan for her treatment would not be interfered with and that injurious studies would not be undertaken.

Methods.—The place chosen for the observations was the physiology department, since adequate measuring apparatus and a quiet room in which outside influences could be partially controlled were available there. Conditions for the observations were maintained as nearly standard as possible. Since it was impossible to control the patient's mood or to put her in a particular one at will, an analysis of her mood was made without her knowledge at the time of each observation. This was done constantly by the same observer, and it was soon clear that her moods fell into several categories which seemed readily classifiable. All possible moods were obviously not represented, and no active attempt has been made to create situations for their effect since it was felt that the artificial factors involved might undermine the confidence of the patient. On the whole, we believed that the external factors were well controlled and that, within limits, comparable observations were carried out.

Recordings were obtained of the motility of the antral region of the stomach by means of a rubber balloon attached to glass tubing which recorded on a smoked drum by means of a tambour connected to a manometer containing solution of sodium chloride. An attempt was made to insert the balloon to the same point and with the same pressure each time. The secretion of the stomach was allowed to flow out of the fistula by gravity and was collected in a glass beaker. The gastric juice was analyzed for combined and free hydrochloric acid, pepsin and bile; the general character of the secretion was noted, and subjective sensations, such as hunger pangs and heartburn, which occurred during observation were

recorded. The color of the mucosa was observed by means of a constant light source and compared directly with a Tallqvist hemoglobin scale. All the observations began at 8:00 to 8:30 a.m., and for each the patient had been fasting for approximately twelve hours unless otherwise indicated.

Findings.—Several control observations were made in the hope of determining the behavior of the stomach in standard circumstances. As indicated previously, these were done under constant environmental conditions, and the patient's mood was recorded at the time of each observation. On this basis, seven observations over periods ranging from one to three hours each were made during which the patient appeared cheerful, happy and cooperative. In the following presentation these normal or control studies will be compared with three studies made during periods of emotional tension. To clarify the description of our findings, several subheadings will be used.

Motility: In five of the seven control observations the motility followed a characteristic pattern. Cyclic activity occurred, with the cycles ranging from fif-

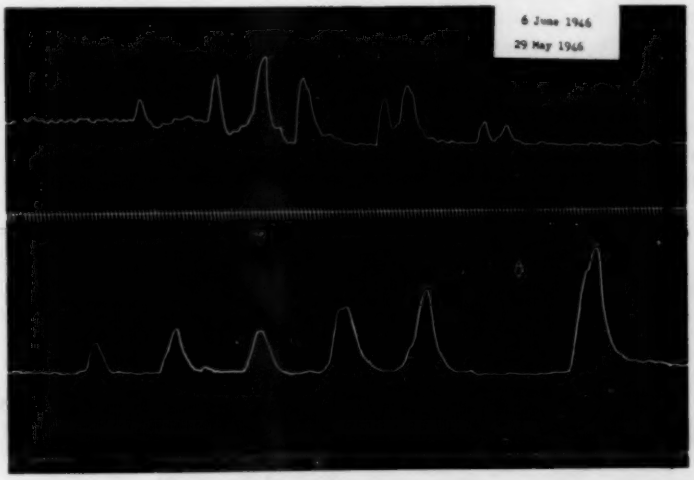

Fig. 2.—Photographs of kymographic recordings of normal peristalsis in the antrum of the stomach on two occasions which illustrate common types of contractions. Time is recorded at second intervals, and a complete cycle is shown in each recording. Note in the lower recording a gradual increase in the amplitude of the peristaltic wave, with no increase in the tone of the stomach as indicated by the base level of recording.

teen to forty-five minutes apart. Occasionally isolated contractions would occur. Two types of contractile activity were observed by us. The higher, rhythmic waves of contraction advancing toward the antrum were noted to be peristaltic in type and seemed to have a propulsive effect on the balloon (fig. 2) The other type was an irregular contraction of lesser magnitude, and it can best be described as a massage or mixing type of activity. We did not note changes in the tone of the stomach with increasing amplitude of contractions. This is clearly illustrated in the lower recording in figure 2. There is no gradual increase to a state of tonic contraction such as has been observed in the male by Wolf and Wolff.[4] Most of the contractions seen at the time of the control observations were of the peristaltic type, and during activity they would occur at the rate of two to three per minute. The average recorded duration of the contractions was usually fif-

teen seconds. In two of the seven observations no motility at all was recorded during a period of three hours. No reason for this lack of motility was apparent. In the determination of the degree of motility of the stomach, the average number of contractions per unit of time was used, with the entire period of the observation entering into the calculation. On this basis, it was found that contractions occurred at the average rate of one every 3.4 minutes during the four periods of observation in which the typical peristalsis was observed (fig. 3). However, several incidental factors were noted which were of interest. Any distention of the recording balloon led to an immediate local contraction of the stomach. This usually subsided quickly and did not influence or initiate any cyclic type of activity. This is in agreement with a similar observation made by Carlson on Mr. V.[3] However, Wolf and Wolff failed to obtain a similar result.[4] Distention, they found, was followed either by relaxation or by a change in the level of the base line of recording.

When appetizing food was shown to Doris, it was found to cause a contraction of the stomach wall, which subsided quickly and did not continue. During one observation, she reported hunger pangs at a time when no contractions were recorded. At another time she complained of cramping pain during exceptionally strong contractions of the stomach, followed by a feeling of hunger. We, as well as Wolf and Wolff, therefore are unable to confirm Carlson's observation that the sensation of hunger is always accompanied with contraction of the stomach.

Secretion: The charcater of the gastric secretion was rather constant. Usually it was mucoid in character, and in some instances it was slightly bile-tinged. It also appeared that with increased motility the rate of secretion increased. This may have been the result of better emptying of the stomach with increased tone, but this seems unlikely inasmuch as free flow occurred at all times. At any rate, the amounts were purely relative since the entire gastric secretion was never obtained. It was interesting to note that the amount of secretion seemed to have a direct relation to the color gradient of the gastric mucosa. As has been noted, the color gradient was obtained by direct comparison of the gastric mucosa with a Tallqvist hemoglobin scale. The amount of secretion increased with an increase in the color gradient. For example, on one occasion on which there was an average color gradient of 70 the secretion collected during a period of seventy-five minutes was 64.4 cc., with 60 degrees of free hydrochloric acid and 18 degrees of combined acid, or a total of 78 degrees of hydrochloric acid. Study of motility showed an average of one contraction in two minutes. This observation was made the third day of menstruation. On a second occasion, when the color gradient averaged 55 the secretion was 55 cc. in ninety-five minutes or 43.5 cc. in seventy-five minutes. Some of this secretion contained bile, with no hydrochloric acid and 10 to 15 degrees of combined hydrochloric acid. There was one contraction every two and a half minutes. On a third occasion, when there was an average color gradient of 45 to 50 the collected secretion over a period of one hundred and ten minutes was 16 cc., with no free hydrochloric acid and 15 degrees of combined acid. No motility was noted during this observation. All these observations were made while the patient was considered to be in a cheerful and cooperative mood. The average color gradient was 50 to 55, with a maximum of 75 and a minimum of 40. The lower color gradient, when it appeared, was present for only short periods. Periods of sleep during the observations appeared to have little or no effect on the color, secretion or motility.

In contrast, three observations were made at times when Doris was disgusted, sullen and angry. This mood was due to what appeared to her as procrastination

and neglect in her treatment. When she was seen in this mood, no attempt was made to change it until after an observation had been made. The accompanying table records seven typical observations indicating the reactions of the stomach to various moods. In experiment 1 the increased acid is probably due to a recent feeding which had to be evacuated from the stomach. The increased motility in experiment 2 as compared to 1 and 3 is probably due to discomfort. The contractions occurred during the first fifteen minutes of the observation, with no contractions during the remainder of the observation. The most constant changes noted are increased motility and increased color gradient when the mood was one of happiness. It is better to examine these three observations separately.

When the observation was made on Feb. 4, 1946, Doris was found to be disgusted with the whole situation, as well as being obviously disappointed. She had been fed two and a half hours before on this occasion, but her stomach was emptied for a control period. The motility of her stomach was found to be

Reaction of the Stomach to Various Moods

Experiment	Condition of Stomach	Mood	Motility (Contractions Per Hr.)	Secretion (Cc. per 5 Min.)	Acid†		Color
					Free	Combined	
1	Not fasting*	Angry and resentful	5	1.1	50	20	45
2	Fasting 12 hours	Angry and resentful	20	2.5	0	39	35
3	Fasting 12 hours	Angry and resentful	6	0.8	0	10	45
4	Fasting 12 hours	Happy	10	2.7	0	39	50
5	Fasting 12 hours	Happy	19	3.3	60	18	65
6	Fasting 12 hours	Happy	23	1.4	30	10	50
7	Fasting 12 hours	Happy	25	3.0	0	15	55

*Liquid feeding given one hour before was evacuated from the stomach prior to observation.
†Measured in degrees of hydrochloric acid, 1 degree being the amount neutralized by 0.1 cc. of tenth-normal sodium hydroxide.

markedly depressed, peristalsis occurring only when she was shown some appetizing food. This peristalsis quickly subsided, however. The secretion which had measured only 26 cc. in the previous hour, increased to 20 cc. in the first ten minutes after appetizing food was tasted. The secretion before and after the patient saw appetizing food contained 50 degrees of free acid and 20 degrees of combined acid even though none of the food reached the stomach at any time. The color gradient of the mucosa was not accurately followed every five minutes during this particular observation, but it was noted that after being told of a proposed operation the patient showed a response of moderate fear and the color gradient of the gastric mucosa decreased from 50 to 40 (experiment 1).

A somewhat different picture was seen on Feb. 6, 1946, at which time Doris was sullen and defiant and on the point of refusing to submit to the observation. Her answers were short, and she was extremely uncommunicative. She did what she was asked to do but obviously under protest (experiment 2).

At this time the motility was cyclic in type, with large peristaltic contractions occurring in three cycles during a period of seventy minutes. During the periods of activity, the contractions occurred every thirty seconds, with a total of twenty-four contractions, or approximately an average of one every three minutes. Doris complained of cramping pains with some of the stomach contractions and a pronounced feeling of hunger which was present after the contractions stopped. The color gradient was exceedingly low during this observation, i.e., 30 to 35, as was the secretion, except during the period when the hunger contractions were occurring, at which time the color gradient increased to 45 and the amount of secretion increased markedly. After the subsidence of motility, the color gradient fell again to 30 and the secretion became meager in amount. The secretion was thick in character and was grossly bile tinged. No free acid and 30 degrees of combined acid were found in the specimen of secretion.

On May 3, 1946, the patient was again found to be upset and disgusted because of what she considered procrastination in her care. This observation was made on the third day of her regular menstrual period. In spite of her mental

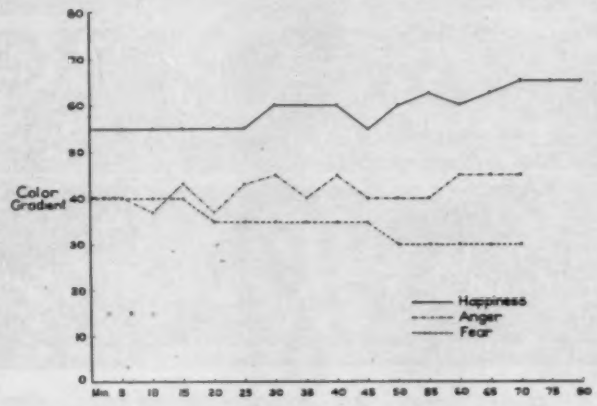

Fig. 3.—A composite graph of the observations of the color of the gastric mucosa (i.e., color gradient) made during periods when the patient was happy, angry and fearful. Note that happiness is associated with a greater color gradient than anger or fear. This is in contrast to the usual observations made on male patients.

state, she was cooperative. During the early part of the observation, the stomach was found to be active for a period of approximately fifteen minutes. The contractions were of the message type rather than peristaltic, being low in amplitude and of much higher frequency. The rate was five to seven per minute. These probably were secondary to the pain associated with insertion of the recording balloon. After cessation of this activity, no further activity occurred for a period of one hour. The secretion was small in amount, measuring 25 cc. in one hour and forty-five minutes. The color gradient ranged between 40 and 45, with little variation. The secretion was mucoid and yellow. No free acid and 10 degrees of combined acid were found (experiment 3).

These observed effects are interesting in view of their variance from those noted by Wolf and Wolff. They found that anger, resentment, hostility, anxiety and sustained emotional tension led to hyperemia, hypersecretion and hypermotility of the stomach. Fear and depressing thoughts led to depressed secretion and motility and to blanching of the mucosa. Our patient showed depressed se-

cretion and motility and blanching of the mucosa not only when she was fearful but at each time when she was considered to be angry, resentful and anxious as to the outcome of her treatment.

Effect of Menstruation: Two observations during the control period were made on the third day of the patient's menstrual periods (Feb. 25 and May 3, 1946). On February 25, however, she was cooperative and happy, while on May 3 she was disgusted and disappointed. Apparently the only common factor was a short period of increased motility, although it varied somewhat in type. As to secretion, hydrochloric acid and color gradient, opposite ends of the scale were reached; they followed the mood rather than the menstrual phase. From the small number of observations made, little correlation with the menstrual period can be made.

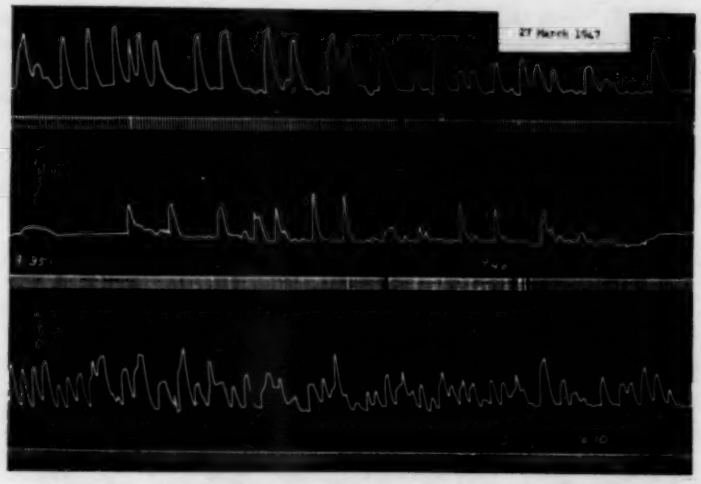

Fig. 4.—A photograph of actual kymographic recordings, showing the response to a painful stimulus. Time is recorded in seconds. The upper recording was made during the period immediately following the insertion of the latex balloon into the pyloric antrum, which caused moderate pain. The increased and rather irregular motility can be compared to that demonstrated by the middle recording, which shows a cycle of motility recorded fifteen minutes later while the patient was free of pain. The lower recording was made later during the same observation at a time when there was pain induced by a rather difficult venipuncture. As can be noted, pain caused a decided increase in motility of the stomach.

On several occasions attempts were made to pass catheters through the cardiac sphincter of the stomach into the esophagus by means of a specially constructed instrument similar to an extremely large sigmoidoscope. This was successful on 2 occasions. During these procedures several observations were made which may be of interest. The cardia was radially scarred but showed a definite rhythmic type of motility. Slow waves of contraction and relaxation occurred, but it was impossible to determine through our instrument whether they were propagated onto the stomach wall. The rate was similar to that observed in the stomach, however, and there were periods when no motility was observed in the cardiac sphincter.

When a catheter was placed in the cardiac sphincter and slight pressure applied, severe retching and heartburn occurred. A considerable increase in bile-

stained secretion also occurred, presumably due to regurgitation through the pylorus. It would stop immediately with removal of the catheter. The stimulus apparently was mechanical, since the onset and the end of the symptoms occurred immediately with pressure changes, although the catheter could be left in contact with the mucosa. A smaller gage catheter could be passed without producing nausea or retching and causing only transient heartburn.

The pylorus was also observed on several occasions, but it was found to be closed at the time of each observation.

During the course of subsequent observations, it was noted that painful stimuli, such as venipuncture, muscle cramps or the insertion of the recording balloon, which usually caused mild discomfort, were nearly always followed by a striking increase in the motility of the stomach. Secretion and color gradient were apparently not altered. Relief of the pain usually resulted in the return of the stomach to a state of activity comparable with the state existing before the painful stimulus was experienced (fig. 4).

SUMMARY

Direct observations of the interior of the stomach were made through a large gastrostomy opening in a 21 year old Negro woman.

A cyclic motility was observed. The interval between cycles and the magnitude of contractions varied considerably. Two types of contraction were seen, i.e., a basic kneading type and a peristaltic type. A cyclic type of motility at the cardiac sphincter was noted.

Under standard conditions, with the patient fasting and in a happy and cooperative mood, a moderately active, secreting stomach with a relatively red mucosa was observed.

Anger, resentment, fear and anxiety were associated with decreased motility and secretion of the stomach and with blanching of the mucosa. It was also noted that the secretion had a lower hydrochloric acid content.

Heartburn, nausea, retching and a reflex of bile-stained secretion were caused by mechanical stimulation in the region of the cardiac sphincter.

Menstruation did not have any appreciable effect on the observed behavior of the stomach.

Periods of sleep appeared to have little effect.

Painful stimuli caused a pronounced increase in the motility of the stomach but had little effect on the secretion or on the color gradient.

The absence of hypersecretion and hypermotility under conditions of sustained emotional tension in this patient was in striking contrast to their presence in male patients previously studied.

EFFECT OF INTRAVENOUSLY ADMINISTERED AMINO ACIDS ON THE STOMACH OF A WOMAN WITH A GASTRIC FISTULA

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THE PURPOSE of this study was to observe directly the effects on the stomach of giving various fluids intravenously, especially those used frequently for intravenous feeding. These observations were made on the interior of the stomach of a 21 year old Negro woman, D. B., through a large gastrostomy opening 6 cm. in diameter.

METHOD OF PROCEDURE

The motility of the stomach was recorded by means of a rubber balloon (condom) which was connected through a glass tubing with a manometer filled with solution of sodium chloride which in turn was connected to a tambour for kymographic recording. Gastric juice was allowed to flow by gravity into a glass beaker by having the patient lie on her left side. Values for hydrochloric acid were obtained by titration with tenth-normal sodium hydroxide, Toepfer's reagent and phenolphthalein being used as indicators. Pepsin values were obtained by the Metz method. The blood flow was expressed as a color quotient, which was expressed in terms of hemoglobin concentration by direct comparison of the gastric mucosa with a Tallqvist scale. For all observations standard conditions were maintained; the patient had been fasting for twelve hours and was cooperative and happy except on occasions indicated.

After control periods of observation, various fluids were given intravenously. These included (1) a solution containing 5 per cent hydrolyzed protein ("amigen") with 5 per cent dextrose and 2 Gm. of sodium chloride per liter (given on two occasions), (2) a solution of crystalline amino acids (Merck & Co.) in 5 per cent dextrose, (3) a solution of 10 per cent dextrose in water, (4) a solution of 10 per cent dextrose in water, containing 2 Gm. of sodium chloride in 1,000 cc. and (5) isotonic solution of sodium chloride. The patient was somewhat fearful of the venipuncture because of previous experiences, but her reaction was relatively constant for all the fluids given, and the effect was thought to be essentially the same in each instance. No attempt was made to hide what was going to be done except that no indication was given of which fluid was being injected.

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FINDINGS

1. Two observations were made during the intravenous injection of 1 liter of fluid containing 5 per cent hydrolyzed protein ("amigen") and 5 per cent dextrose with 2 Gm. of sodium chloride. On May 20, 1946, the patient was as usual apprehensive at the prospect of a venipuncture, but she was cooperative. She had been fasting for twelve hours. There was a fifty minute control period before the administration of "amigen" was started, and during it the stomach was active, undergoing contractions of the peristaltic type that were cyclic in character, occurred at a rate of two per minute and lasted fifteen to twenty seconds. There was a total of forty-five contractions in fifty-five minutes. The color gradient was 45 to 50, and the secretion was 20 cc. in forty minutes; the latter contained no free hydrochloric acid and 24 degrees of combined hydrochloric acid.

Immediately after the start of the injection of "amigen" the motility continued, but the earlier slow, rhythmic, propulsive type was replaced by nonpropulsive, massage-like contractions. This effect was probably due to the pain of the venipuncture, as it was similar to that observed at other times after painful stimuli, i.e., the curves showed a more irregular but more rapid rate of contractions of lower amplitude. The type of contractions described gradually decreased in amplitude until they disappeared completely thirteen minutes after the administration of "amigen" was started; they did not recur until approximately two minutes after administration was discontinued fifty minutes later. This recurrence was assumed to be due to the pain of removing the needle.

The rate of flow at the start was 15 cc. per minute, which is more rapid than usual. The faster rate was chosen to observe the effect of nausea, which frequently follows after such a rapid rate of administration. As was expected, the patient complained of feeling slightly nauseated when approximately 200 cc. had run in. The stomach in the meantime had become quiescent, and the secretion had fallen off sharply, was almost entirely mucoid in character and contained bile. The patient became quiet as though she were alsleep. She then complained of thirst; the color gradient was measured and found to be 30. During all this time, the secretion was extremely meager. At no time during periods in which she complained of nausea was there any motility of the stomach even though there was considerable salivation.[1] No free acid and 36 degrees of total hydrochloric acid were found in the gastric secretion.

A second injection was given on June 7, 1946, which was on the second day of the patient's regular menstrual period. Although fearful

1. Wolf., S.: The Relation of Gastric Function to Nausea in Man, J. Clin. Investigation **22**:877-882, 1943.

of the pain produced by the needle, she was cooperative and cheerful. During a thirty minute control period the stomach was exceedingly active and showed the usual contractions. The color gradient was 40 at the onset and gradually fell to 30. No free acid and 26 degrees of combined hydrochloric acid were found in the gastric secretion during the control period.

After the needle was first introduced, the stomach showed the same changes as those described previously, which were interpreted as being due to the pain stimulus. After this period of activity, there was complete quiescence except during one or two short intervals in which the amount of secretion gradually dropped to zero, with the color gradient remaining at 30. There was also no change in the hydrochloric acid content. Determinations of pepsin content made at the same time showed a drop to one third of the fasting level. This finding may be questioned, however, since the pepsin content of the specimen obtained when the stomach was first emptied was twenty times as high as that in the specimen obtained after "amigen" was given. Practically no nausea was observed during this injection, which was due to the slower rate of injection (10 cc. per minute). In summary, at the time of both observations there was a cessation of preexisting motility and a decrease in secretion, without any appreciable change in the acid content but with a decrease in the pepsin content.

2. One observation was made on May 29, 1946, on the use of 10 per cent dextrose in water. The patient's mental state was little changed from that found at the time of the other observations. She apparently had been angry with one of the nurses before coming to the laboratory, but she was in good spirits at the time. A control period of approximately thirty minutes was observed. The patient had taken a small amount of food five hours before, but this was removed completely before the observation was begun. During the control period, typical cyclic peristalsis was seen. The secretion was small in amount and rather thick and mucoid in character. It was bile tinged and contained no free acid and 58 degrees of combined hydrochloric acid. The color quotient was found to be 40 to 45.

After the injection was started no change could be seen in the motility with the exception of a slight increase in the rate of contractions. There was little change in the amount of secretion, two specimens containing 30 and 55 degrees of combined acid respectively. The pepsin content, however, was observed to drop to one third of the fasting value. No change in the color quotient was noted. The patient's only complaint during the observation was of a full feeling in her stomach and a transient chilly sensation. The rate of flow was controlled as nearly as possible at 15 cc. per minute. In summary, no change was observed during the injection of 10 per cent dextrose in water.

3. One observation was made on the use of 10 per cent dextrose in water to which was added 2 Gm of sodium chloride to give a solution osmotically equivalent to the "amigen" solution previously used. At the time of the injection of this solution, the patient was recovering from a slight cold and said she had not been felling as well as usual. During the control period, the color gradient was found to be somewhat high (55 to 60), and typical intermittent cyclic contractions of the peris-

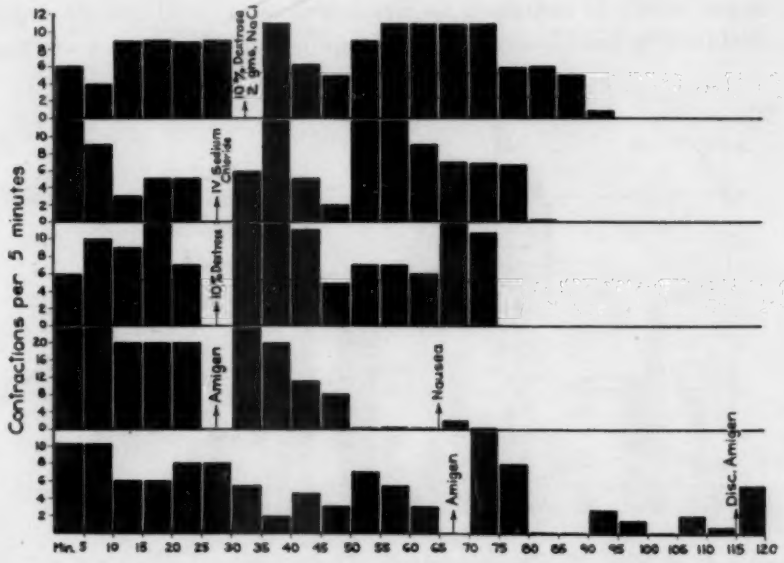
Contractions per 5 minutes
10% Dextrose gms. NaCl
N
IV Sodium Chloride
10% Dextrose
Amigen
Nausea
Amigen
Disc. Amigen
Min. 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120

Fig. 1.—Diagrammatic representation of gastric motility during the intravenous infusion of various fluids. The number of contractions every five minutes is plotted against the time at five minute intervals. The arrows indicate the onset and end of the infusions. The top graph indicated little change during the period of infusion of 10 per cent dextrose containing 2 Gm. of sodium chloride per liter as compared with the previous control period. In graphs 2 and 3 there is little change noted during the infusion of sodium chloride or 10 per cent dextrose. In graphs 4 and 5 definite decrease in motility is noted during the administration of "amigen." The initial increase in motility in each instance at the onset of the infusion is presumably due to the pain of the venipuncture.

taltic type occurred in the stomach. The secretion was small in amount and was bile stained. No free hydrochloric acid and 31 degrees of combined hydrochloric acid were found. The pepsin content was noted to be markedly decreased in comparison with that of the specimen which was obtained at the beginning of the observation. After the solution was started the color gradient remained constant at 55 and the secretion varied little in amount and remained thick, mucoid and bile tinged. The motility of the stomach continued unchanged. There was still no free hydrochloric acid, and the combined hydrochloric acid content fell to 13 degrees. Also no pepsin was found in the secretion. In summary,

there was the same lack of effect as was noted with the use of 10 per cent dextrose in water.

4. One observation was made on June 6, 1946, a liter of isotonic solution of sodium chloride, injected in a similar manner, being used. The patient was feeling well, and except for the usual apprehension connected with the procedure she was in a cheerful and cooperative mood. During the control period of forty minutes the color gradient was 40 to 45 and the secretion was moderate in amount, mucoid in character and of an amber color. It contained no free hydrochloric acid and 28 degrees of combined hydrochloric acid. The pepsin content was at a relatively

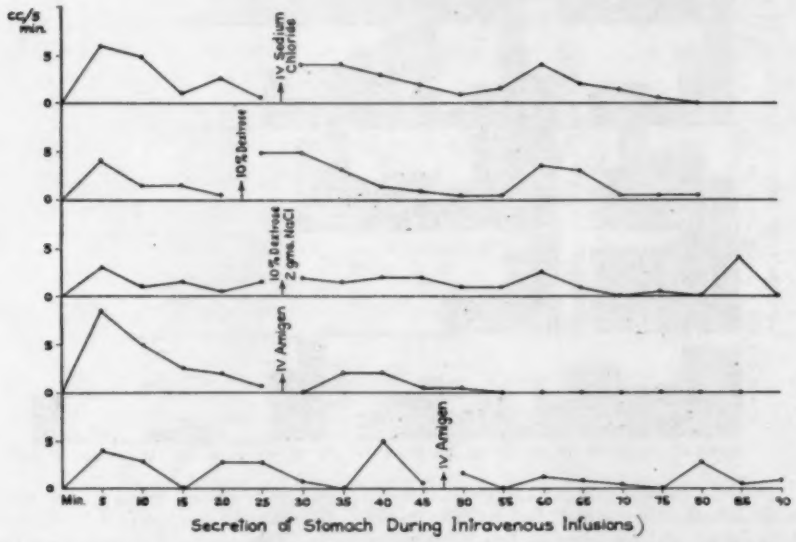
cc/5 min.
5
0
IV Sodium Chloride
10% Dextrose
10% Dextrose 2 gms. NaCl
IV Amigen
IV Amigen
Min. 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Secretion of Stomach During Intravenous Infusions)

Fig. 2.—Representation of the amount of secretion in cubic centimeters per five minutes during the intravenous infusion of various fluids. The time is recorded in minutes. The arrows indicate the onset of the infusions. In the top graph little change can be noted with the infusion of sodium chloride. Administration of 10 per cent dextrose and of 10 per cent dextrose containing 2 Gm. of sodium chloride per liter had little depressant effect on the gastric secretion (graphs 2 and 3). In graphs 4 and 5, however, a decided decrease in the gastric secretion during the administration of "amigen" is shown.

low level. The stomach showed typical contractions. With the beginning of the injection, the activity continued unchanged. Secretion continued at approximately the same rate as during the control period, but the combined hydrochloric acid content in the secretion fell to 15 degrees, the free hydrochloric acid remaining absent. The pepsin content fell slightly, but the final specimen was comparable to the one obtained at the beginning of the observation. The color gradient remained constant at 40. In summary, the sodium chloride appeared to have relatively little effect.

5. One observation was made on the use of a solution of crystalline amino acids (Merck & Co.) in 5 per cent dextrose injected intravenously. At the time of the observation the stomach showed typical motility. The color gradient varied from 30 to 35, and the rate of secretion was approximately 3 cc. in five minutes. The secretion contained 12 units of free and 7 units of combined hydrochloric acid. The pepsin content was 6.5 units.

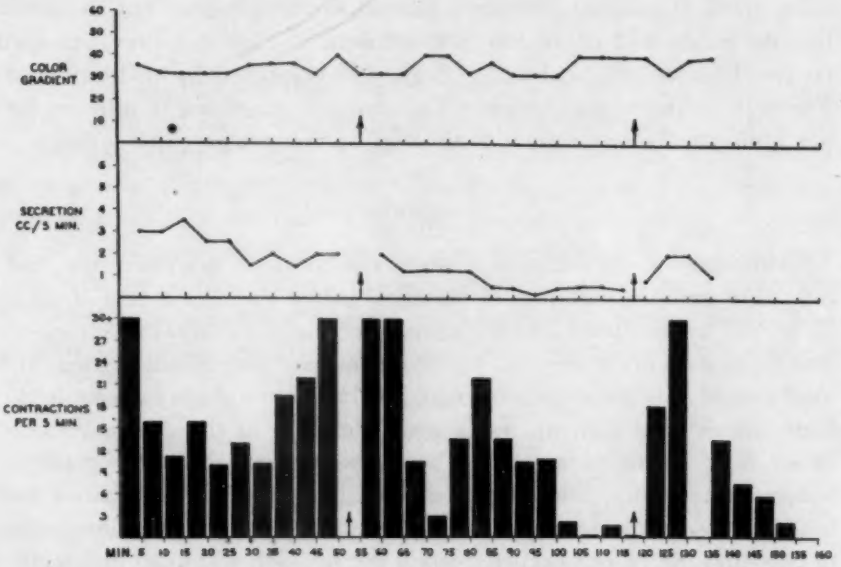

Fig. 3.—Composite graph of the effects on the stomach of the administration of a solution of crystalline amino acids. The time is recorded in minutes. In the top graph it is noted that the color gradient of the gastric mucosa remained low during the entire observation, no particular change occurring with the infusion. In the middle graph a definite decrease in the amount of gastric secretion is noted during the infusion of the amino acids. In the lower graph the motility is seen to be definitely depressed during the infusion. The effect of pain altered the picture somewhat. Immediately after the arrow which indicates the venipucture, there is a marked increase in motility secondary to the pain. After seventy-five minutes there is a sudden increase in motility concomitant with a complaint of severe aching in the wrist and hand. The aching was relieved by warming, and motility subsided. The pain recurred, however, and became so severe that the infusion was discontinued (second arrow). A pronounced increase in motility again occurred with the severe pain.

Immediately after the venipuncture, there was considerable pain, and the motility of the stomch showed the previously described changes. During the next ten minutes, motility decreased considerably, which was similar to the effect observed with "amigen." However, during the next fifteen minutes the patient complained of pain in her forearm, and immediately the motility increased to approximately the original level. She then became free of pain and was comfortable; this feeling was accompanied with subsidence of motility. The pain in her arm then

became so severe that the injection had to be discontinued. Motility was again increased during this period of discomfort. The pain was apparently due to overdistention of the veins of the forearm since the venous return was decreased by venous thrombosis as a result of previous venipunctures.

During periods in which there was no pain, motility was depressed by the intravenous injection of solution of crystalline amino acids. The color gradient was not materially altered by the infusion, but the secretion decreased to 1 cc. or less in five minutes. This secretion contained no free hydrochloric acid and 5 degrees of combined hydrochloric acid. The pepsin content was 3.6 units. In summary, the effects of pure crystalline amino acids were similar to those of hydrolyzed protein ("amigen").

COMMENT

Although but six complete observations are here described, the findings were uniform. Solution of "amigen" when given at a rate of 10 or 15 cc. per minute produced the same effect on the two occasions except that nausea occurred on one. Motility decreased and finally ceased, and total gastric secretion decreased, with no change or a slight increase in the hydrochloric acid content and a probable drop in the pepsin content. Blood flow decreased as shown by a lowering of the color gradient. Subjective reactions, consisting of mild chilly sensations with nausea and headache, were the result of too rapid administration. It is interesting to note that the nausea occurred when the stomach was quiet and secreting slowly even though there was profuse salivation. This is in agreement with the findings of Wolf on the reaction of the stomach to nausea produced by vestibular stimulation. A 5 per cent solution of crystalline amino acids in 5 per cent dextrose produced a similar secretion of the gastric mucosa, a decrease in the free and combined hydrochloric content and a decrease in the pepsin secretion. This suggests that the depressant effect of "amigen" was due to the content of amino acids.

Three control observations were made, one each on the use of 10 per cent dextrose in water, 10 per cent dextrose in water which contained 2 Gm. of sodium chloride in each 1,000 cc. and with isotonic solution of sodium chloride. In no case was the motility or the total secretion affected. The hydrochloric acid and pepsin contents in the gastric secretion decreased, however. No change was noted in the mucosal color.

It would seem logical to assume from these observations that the amino acids when introduced intravenously decrease gastric motility and secretion and the production of pepsin, whereas other solutions containing only dextrose or sodium chloride seem to cause only a slight de-

crease in the production of hydrochloric acid and pepsin. Inasmuch as rest of the stomach is advantageous, it is reassuring to know that parenteral feeding with amino acids not only does not stimulate the stomach but actually decreases its normal resting activity. The effect of pain produced by the act of introducing the needle intravenously and by venous distention was invariably one of gastric stimulation and has been referred to in a previous paper.

SUMMARY

Gastric function was observed in a young woman with a large fistula which permitted direct observation of the interior of the stomach. The intravenous administration of a 5 per cent solution of either hydrolyzed protein ("amigen") or crystalline amino acids in 5 per cent dextrose was found to decrease motility and secretion. Inhibitory effects on gastric function were not observed during injections of 10 per cent dextrose with or without sodium chloride or of isotonic solution of sodium chloride. It is concluded that the intravenous injection of amino acid mixtures depresses gastric function and thus promotes gastrointestinal rest.

COMPLETE STRICTURE OF THE EXTRAHEPATIC BILE DUCTS

External Hepaticostomy Followed By Spontaneous Hepatoduodenal Fistula

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WE WISH to report 6 cases of complete stricture of the extrahepatic bile ducts in which external hepaticostomy was followed by the spontaneous development of a hepatoduodenal fistula. In 5 of these cases no effort was made to create an anatomic condition which would favor the development of such a fistula. A rubber catheter was sutured into the intrahepatic duct to create an external biliary fistula in the first 2 cases. It was the intention of the surgeon (W.W.) to transplant the fistulous tract into the intestine at a later date, but a fistula developed between the bile duct and the intestine in the interim. Owing to the gratifying result obtained in these cases, one of us (W.W.) decided to use a similar surgical procedure in the next case of complete stricture of the extrahepatic bile ducts in which an anastomosis could not be effected between a patent bile duct and the intestine. In case 6 the duodenum was brought up and sutured to the liver so that the catheter would press against its wall. It was hoped that the pressure of the catheter on the wall of the duodenum would cause necrosis which in turn would result in the development of a hepatoduodenal fistula.

As far as we know, the use of this type of surgical procedure never has been advocated in cases of stricture of the common bile duct or the hepatic duct. The procedure may be carried out in cases of complete stricture of the common bile duct in which the remaining portion of hepatic duct or ducts is too short to permit the surgeon to perform hepatoduodenostomy.

REPORT OF CASES

CASE 1.—A man aged 60 years had undergone a cholecystectomy on Jan. 29, 1930. An external biliary fistula had developed after the operation. This had been followed by the occurrence of jaundice, chills and fever. Choledochostomy had been performed on Jan. 12, 1931. A catheter had been inserted in the common bile duct and had been permitted to remain in place for three months. Jaundice, chills and

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fever had occurred after this operation. In January 1935 the patient came to the clinic because of these symptoms.

Laparotomy was performed by one of us (W.W.) on Jan. 14, 1935. The operation disclosed a complete stricture of the extrahepatic bile ducts. The intrahepatic portion of the hepatic duct was dilated and contained twenty small stones. A rubber catheter was sutured into the duct. It was hoped that this would result in the formation of an external biliary fistula which could be transplanted into the intestine at a later date. Before the patient was dismissed from the hospital a small amount of fecal material drained from the abdominal incision. Healing occurred spontaneously.

Three months after the operation the patient noticed that his stools were colored. A fistula had developed between the biliary tract and the intestine. Five years later the patient died of a cerebral hemorrhage. In the interim he had only two or three attacks of mild jaundice, which were of short duration.

Case 2.—A woman aged 49 years had undergone a cholecystectomy in June 1935. Jaundice had developed after the operation, and a choledochostomy had

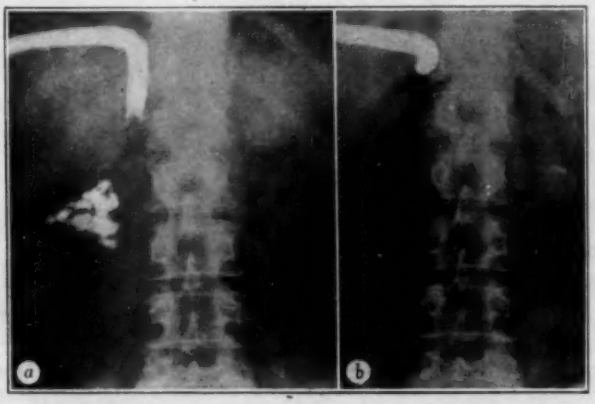

Fig. 1.—Cholangiograms made after external hepaticostomy in case 1. *a*, contrast medium is entering the duodenum freely, which indicates that a hepatoduodenal fistula has formed; *b*, ten minutes after injection of the contrast medium it is dispersed throughout the small intestine.

been performed in June 1937. The jaundice had recurred after this operation. The patient came to the clinic on Jan. 10, 1938. On January 20 laparotomy disclosed complete stricture of the extrahepatic bile duct. An external biliary fistula was established by suturing one end of a rubber catheter into the intrahepatic duct and bringing the other end out onto the surface of the abdomen. The patient went home in March 1938. She returned to the clinic on Dec. 7, 1938, and stated that in September she noticed some particles of food coming through the catheter. Her stools acquired a normal color. Bile stopped draining through the catheter.

On December 10 cholangiography was performed by injecting contrast medium into the fistulous tract. This examination disclosed that a hepatoduodenal fistula had developed (fig. 1). In a letter received in March 1945 she said that she was having recurring mild attacks of cholangitis without pain.

Case 3.—A woman aged 43 years had undergone a cholecystectomy in June 1941. Jaundice had developed one week later. A biliary fistula had developed and had produced some remission of the jaundice. On Feb. 24, 1942, the pa-

tient came to the clinic because of jaundice, pruritus and intermittent attacks of chills and fever. The value for the direct reacting serum bilirubin was 36.3 mg. per hundred cubic centimeters. On March 31 laparotomy disclosed an extensive stricture of the common bile duct. It was observed that a fistula was about to develop between the hepatic duct and the duodenum. A hepaticoduodenostomy (end to side) was performed over a Mayo-Sullivan tube. After the operation the patient had frequent transitory attacks of jaundice but she did not have any fever. In November 1945 the patient had an attack of jaundice after an attack of cystitis. The icteric discoloration deepened and persisted. When she was seen on Jan. 19, 1946, the value for the direct reacting serum bilirubin was 42 mg. per hundred cubic centimeters. Laparotomy was again performed on Feb. 1, 1946. The operation disclosed complete stricture of the extrahepatic bile ducts, hepatitis of grade 3 on the basis of 1 to 4 and cirrhosis of the liver. External hepaticostomy was performed in the same manner as it was in the previous case. In June 1946 the patient noticed that bile had ceased to flow from the catheter and that her stools had become colored with bile. The catheter was removed. Since the removal of the catheter the patient has had two attacks of transient jaundice but her health otherwise has been good. She was examined in the clinic on Nov. 25, 1947, and was in excellent condition. With the exception of a slight icteric tinge to her scleras she had no jaundice. Her liver was barely palpable below the costal margin. Her blood count was normal, and the values for the direct and indirect reacting serum bilirubin were 2.1 and 1.0 mg. per hundred cubic centimeters. Chemical examination of the blood disclosed the following values: serum protein 7.5 gm. per hundred cubic centimeters and cholesterol 240 mg., fatty acids 378 mg., and total lipids 618 mg. per hundred cubic centimeters of plasma.

She had had, however, episodes of pain in the right upper quadrant, chills and a temperature of 101 to 103 F., dark urine and clay-colored stools in the three month interval from September to November 1947.

Case 4.—A woman aged 44 years had undergone a cholecystectomy in March 1946. Jaundice had developed two weeks later. On May 23, 1946, she came to the clinic because of intermittent attacks of jaundice and pruritus. On June 3 laparotomy disclosed a complete stricture of the extrahepatic bile ducts. External hepaticostomy was performed in the same manner as it was in cases 2 and 3, with the hope that an external biliary fistula would develop. She was sent home to recuperate and told to return in two to three months. On July 13, 1946, the patient returned to the clinic because of a recurrence of jaundice. There was drainage of bile from around the catheter. On July 19 a laparotomy was performed. Hepaticostomy was also performed, and a catheter was inserted into the intrahepatic duct and fastened to the liver. In a letter dated April 4, 1947, the patient said that bile still was draining freely from the catheter but that she thought that some bile was passing into her intestine because her stools were medium brown in color. Her general condition was good. She has had an elevated temperature on several occasions but no chills. She has not had any jaundice.

Case 5.—A woman aged 22 years came to the clinic because of jaundice which had been present in varying degrees since January 1945. She also had had intermittent attacks of epigastric pain which had extended to the left and had been associated with chills and fever. She had undergone a cholecystectomy in September 1946. No gallstones were present, but the gallbladder was diseased. Jaundice had persisted after the operation, and the patient had had several attacks of epigastric pain.

The patient was markedly jaundiced when she was examined at the clinic. The value for the direct reacting bilirubin was 10.6 mg. per hundred cubic cen-

timeters of serum. Exploratory laparotomy was performed on Dec. 22, 1946. A remnant of the gallbladder was found. This was opened, but no stones were found. The common bile duct could not be located. A considerable amount of bleeding occurred in the course of the operation; this was controlled by inserting a gauze pack between the liver and the omentum. The pack was removed ten days later. On the fourteenth day after the operation a catheter was inserted through the sinus tract which had been occupied by the pack. Some bile drained from the catheter. The patient was permitted to return to her home with the catheter in place. Small amounts of bile continued to drain from the catheter. Three months after she returned to her home she noticed that her stools were colored.

On May 28, 1947, cholangiography disclosed two pockets of the contrast medium in the soft tissues adjacent to the common bile duct. Each pocket was connected with the common bile duct by a sinus tract. The common bile duct was rather well filled with the contrast medium, which was entering the duodenum freely (fig. 2). Her general condition was good, and there was no evidence of jaundice.

Case 6.—A man aged 46 years had undergone a cholecystectomy and a choledocholithotomy in April 1944. A biliary fistula (external) had developed, and

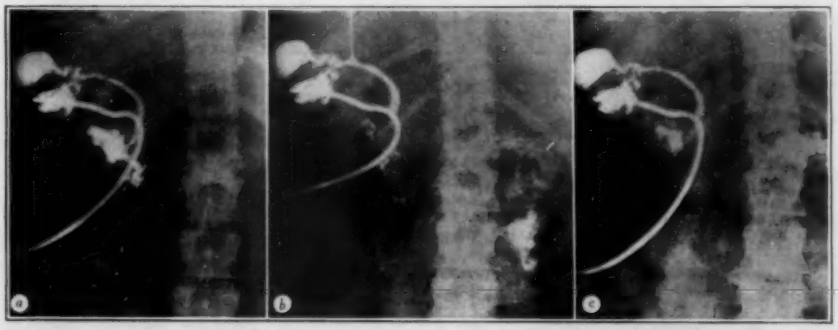

Fig. 2.—Cholangiograms made after operation in case 5. *a*, contrast medium is entering the duodenum freely; *b*, ten minutes after injection of the medium it is dispersed throughout the small intestine; *c*, appearance twenty minutes after injection of the medium.

the patient had become jaundiced. In December 1944 a choledochostomy had been performed, and a T tube had been inserted. The tube had been removed three weeks later. After removal of the tube jaundice and pruritus had developed, the stools had become clay colored and the patient had had occasional attacks of chills and fever. These symptoms had persisted until the patient came to the clinic in January 1947.

When the patient was examined at the clinic, the values for the cholesterol and the cholesterol esters were 143 mg. and 52 mg. respectively per hundred cubic centimeters of plasma. The value for the direct reacting bilirubin was 8 mg. per hundred cubic centimeters of serum, and that for the indirect reacting bilirubin was 2.5 mg. The albumin-globulin ratio of the serum was 1:1.1. The prothrombin time was sixty seconds (normal is seventeen to nineteen seconds) when determined by a modification of the method of Quick. After vitamin K had been administered orally and intravenously for three days, the prothrombin time was found to be twenty seconds. The sedimentation rate of the erythrocytes was 88 mm. in one hour. When analyzed by the method of Watson, a twenty-four hour specimen of feces was found to contain 58 Ehrlich units of urobilinogen.

On Jan. 16, 1947, laparotomy disclosed complete stricture of the common bile duct, the hepatic duct and the extrahepatic portion of the two main ducts which pass out of the liver at the porta. The intrahepatic portion of the two main ducts was identified by means of an aspirating needle. This portion of the ducts was found to be dilated. A rubber catheter was inserted into each of these ducts and fastened with silk sutures. The duodenum was brought up and sutured to the liver. The sutures were tied tightly so that they would cause necrosis, which it was hoped would have a tendency to favor the development of a hepatoduodenal fistula.

Bile drained from both catheters after the operation. The bile which drained from the left hepatic duct was practically colorless; that which drained from the

Concentration of Bile Salts and Bilirubin After Operation in Case 6

Date	In Bile That Drained From Left Hepatic Duct		In Bile That Drained From Right Hepatic Duct	
	Bile Salts, Mg. per 100 Cc.	Total Bilirubin, Mg. per 100 Cc.	Bile Salts, Mg. per 100 Cc.	Total Bilirubin, Mg. per 100 Cc.
Jan. 30, 1947	145.0	1.2	56.5	3.5
Jan. 31, 1947	185.0	4.7	48.3	1.3
Feb. 7, 1947	291.0	11.0	121.0	7.4

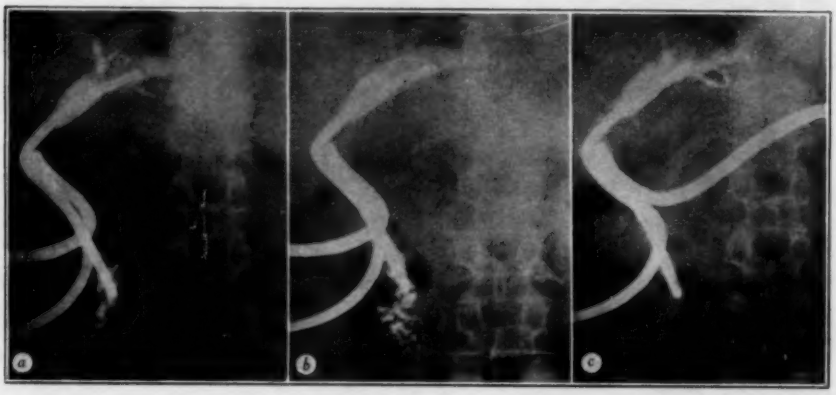

Fig. 3.—Postoperative cholangiograms in case 6. *a*, contrast medium is entering the duodenum freely. One catheter enters the duodenum and the other catheter enters the intrahepatic duct; *b*, ten minutes after injection of the medium it is dispersed in the small intestine; *c*, appearance twenty minutes after injection of the medium.

right hepatic duct had a normal appearance. The concentration of bile salts and bilirubin in bile which drained from the two hepatic ducts was determined on three occasions. The results of these analyses are shown in table 1. The convalescene was uneventful, and the patient returned to his home three weeks after the operation.

When the patient returned to the clinic for a check-up on April 12, 1947, the two catheters were still in place. He had gained in weight and strength. The stools were colored with bile pigment. The urine was of a normal color and did not contain any bile. The value for the direct reacting bilirubin was 3.4 mg. per hundred cubic centimeters of serum. Cholangiography was performed by injecting a contrast medium into each catheter. The medium filled the biliary tree and

flowed into the duodenum. Both catheters were removed, cleansed and reinserted. Cholangiography was performed again on April 13. This disclosed that one catheter followed a sinus tract downward into the duodenum while the other one pointed upward toward the hepatic ducts (fig. 3). Bile was draining freely from the latter catheter. The catheter which was directed downward toward the duodenum was removed, but the other one was permitted to remain in place. The patient was allowed to return to his home, but he was instructed to leave the catheter in place indefinitely.

In a letter dated June 16, 1947, the patient said that the catheter had slipped out and that he had been unable to reinsert it. His stools and urine were of normal color, and there was no drainage from the external biliary fistula. He said that he did not have any signs of biliary obstruction. On August 31 he had an attack of severe epigastric pain. In the previous week he had noticed a return of jaundice which was accompanied with pruritus.

He returned to the clinic on Sept. 5, 1947. It was decided that the lumen of the hepatoduodenal fistula, which apparently had developed in the previous spring, had become narrow and that the patient again had severe obstructive jaundice. On September 11 an exploratory laparotomy revealed a stricture of the fistula between the intrahepatic duct and the duodenum. It was possible to insert one arm of a large T tube into one of the intrahepatic ducts and the other arm in the duodenum. The duodenum was sutured to the hilus of the liver with two silk sutures. We feel that the T tube should be left in place for at least one year.

In a letter dated Oct. 24, 1947, the patient said that he was feeling very well. He was gaining weight, and his stools were of a normal color.

COMMENT

This report is based on 6 cases of complete stricture of the extrahepatic bile ducts in which external hepaticostomy was followed by the spontaneous development of a hepatoduodenal fistula. In the first of these cases no effort was made to promote the development of such a fistula. An attempt was made to create an external biliary fistula which could be transplanted into the duodenum at a later date. A hepatoduodenal fistula developed before the second stage of the operation could be performed.

In case 5 an external biliary fistula was established by inserting a rubber catheter into a sinus tract which had developed after a gauze pack had been applied to control bleeding which had occurred in the course of an exploratory operation. A hepatoduodenal fistula developed spontaneously about three months later.

We wish to call attention to a slight modification of the technic, employed in case 6. In this case the duodenum was brought up and sutured to the under side of the liver. The sutures were tied tightly. It was hoped that this would produce necrosis which would favor the development of a hepatoduodenal fistula. We had expectations that this modification might assist in the development of a fistula into the duodenum, which it did. Unfortunately the fistula closed after the removal of a catheter from the sinus tract.

In 5 of the 6 cases the patients have had few, if any, symptoms of biliary obstruction for periods ranging from six months to eight years after the operation.

CHEMICAL STUDIES ON EXPERIMENTAL HEPATIC CONGESTION IN THE DOG

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IN A RECENT paper[1] two of us (D. K. and T. C. H.) described a method for producing hepatic congestion with accompanying portal hypertension in the dog by a three stage operational procedure. The method involved the partial ligation of the posterior vena cava caudad to the liver and cephalad to the kidneys (stage I), in this way allowing collateral venous pathways already present to become better developed and thus preventing venous congestion. This was followed after a time by a second operation in which the vena cava was completely severed at the point of ligation (stage II) and by a third in which the vena cava just anterior to the diaphragm was partially occluded (stage III). The present paper reports the results of chemical studies on 4 dogs who had been subjected to this procedure. These studies were carried out in an attempt to determine whether congestion of the liver so produced leads to disturbance in hepatic function, as measured by chemical changes in body fluids.

METHOD

The 4 dogs used in the experiments to be described varied in initial weight between 10.3 and 14.6 Kg. Two of the dogs were male, and 2 were female. Throughout the course of the experimental period, which ranged from one hundred and thirty-three to three hundred and ninety-nine days, they were maintained on a diet of one-half pound of "purina" dog chow[2] per day, equivalant to 700 calories.

This work was carried out in the departments of experimental surgery and anatomy, New York University College of Medicine, and was aided by a grant from the Dazian Foundation for Medical Research.

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2. The "purina" dog chow had the following composition: crude (per cent): protein, 23.0 (per cent digestible 19); fat, 5.0 (per cent digestible 4.7); fiber, 4.0; ash, 7.0; nitrogen-free extract, 54.0 (per cent digestible 48); moisture, 7.0.

(Footnotes continued on next page)

During the experimental period, analyses of the following were carried out on the blood: total plasma protein, albumin and globulin levels, nonprotein nitrogen, prothrombin clotting time, fibrinogen content, free and total cholesterol, blood glucose levels, serum phosphatase activity and hematocrit values. In several instances sulfobromophthalein clearance times were ascertained. The ascitic fluid, which was produced in considerable quantity after operation III and which was removed at frequent intervals, was also assayed for total protein, albumin, globulin and free and total cholesterol. Weight changes in the dogs were also recorded. The following procedures were used in carrying out the analyses. Nitrogen was determined by the micromethod of Levy and Palmer[3]; albumin and globulin levels by Howe's[4] procedure modified by use of the angle centrifuge instead of filtration for the globulin precipitate; fibrinogen by the gravimetric procedure of Foster and Whipple[5]; prothrombin clotting time by Quick's method[6]; free and total cholesterol according to the procedure of Schoenheimer and Sperry,[7] the Klett-Summerson photoelectric colorimeter with filter 66 being used instead of the Dubosq colorimeter, and blood sugar by Benedict's[8] modification of the method of Folin and Wu. Blood phosphatase was measured by the method of Bodansky[9] with the Klett-Summerson colorimeter and a no. 42 filter. Sulfobromophthalein clearance teses were carried out according to the method of Rosenthal and White,[10] with the Deutsch modification[11] of using 2 mg. of dye per kilogram and reading

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The mineral analysis was as follows: iron, 0.018 per cent; magnesium, 0.09; silica, 0.23; potassium, 0.56; sodium, 0.67; chloride, 0.68; phosphorous, 1.17; calcium, 2.22; iodine (in form of iodized salt).

The following vitamins were present: A, about 4,000 international units per pound, supplied by cod liver oil, yellow corn and carotene; B, about 275 Sherman units per pound, supplied by wheat germ; C, low; D, about 500 international units per pound, supplied by cod liver oil; E, no measurement; G, 300 Sherman units per pound, supplied by wheat germ, milk, wheat and cereals.

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(Footnotes continued on next page)

RESULTS

Changes in body weight, quantities of ascitic fluid withdrawn, plasma protein levels, albumin-globulin ratios, glucose contents and total cholesterol and free cholesterol levels for each of the 4 dogs throughout the experimental period are shown in figures 1 to 4. The three vertical lines on each graph represent the times at which the operative procedures were carried out. Ascitic fluid was withdrawn to maintain the animals at approximately constant weight. It should be noted that while there was no consistent change in weight after the first two operations a rather notable increase occurred after the third. This is especially evident in dogs 39 and 42. This increase in weight is apparently due to the accumulation of ascitic fluid in the body cavities brought about by the increased hepatic congestion and the consequent back pressure on the whole portal system. The total fluid removed varied for the 4 dogs from 5.2 to 60.2 liters. The values for the individual dogs are shown in table 2. It should also be noted that ascitic fluid did not begin to accumulate in large quantity until approximately two to three months after operation III and was not observable in any instance before seven days. From these results it would appear that a minimum interval of seven days is required to build up sufficient pressure to bring about filtration of measurable quantities of fluid into the body cavity. While only 5.2 liters of ascitic fluid was removed from dog 39 throughout the experimental period, it is interesting to point out that in dog 42 it was necessary in 1 instance to remove almost 8 liters of fluid in the interval of a little more than one week.

The data on plasma protein, albumin-globulin ratio, glucose, total cholesterol and percentage of free cholesterol represented in figures 1 to 4 show considerable variation, and except for the total cholesterol level, which shows a clearcut decrease after operation III, it is difficult to tell by inspection whether any significant changes have occurred. The data were, therefore, treated in the following way: All the results prior to operation III were averaged, as well as all the results after. These averaged results are shown in table1 along with data on albumin and globulin levels, nonprotein nitrogen, prothrombin clotting time, fibrinogen and hematocrit values. The standard deviations for the mean values are also indicated beneath each mean. No standard deviations were calculated when the number of determinations was fewer than six. When the data are represented in this way, it becomes apparent that in all

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11. Deutsch, E.: Fractional Bromsulfalein Test to Determine Liver Damage in Non-Jaundiced Patients, New England J. Med. **225**:171 (July 31) 1941.

after five and fifteen minutes in the spectrophotometer at a wavelength of 580 microns.

TABLE 1.—*Relationship Between the Average Concentration of Various Constituents of the Blood Before and After Operative Procedure III**

Constituent	Dog 39		Dog 42		Dog 44		Dog 45	
	Before	After	Before	After	Before	After	Before	After
Plasma protein (Gm./100 cc.)	6.7(16) 1.1	6.0(34) 0.8	6.3(10) 0.9	4.0(26) 0.7	5.7(3)	4.2(12) 0.3	6.7(3)	4.2(23) 0.9
Albumin (Gm./100 cc.)	4.2(16) 0.9	3.1(34) 0.5	4.1(10) 0.2	2.4(25) 0.1	3.9(3)	2.6(12) 0.4	4.2(2)	2.6(23) 0.6
Globulin (Gm./100 cc.)	2.5(16) 0.5	2.9(34) 0.9	2.2(10) 0.2	1.7(25) 0.2	1.7(3)	1.6(12) 0.4	2.1(2)	1.6(23) 0.5
Albumin-globulin ratio	1.7(16) 0.5	1.1(34) 0.5	1.9(10) 0.9	1.4(25) 0.5	2.3(3)	1.6(12) 0.7	2.0(2)	1.6(23) 0.5
Non-protein nitrogen (Mg./100 cc.)	26.8(11) 2.7	28.8(26) 3.8	28.4(8) 6.4	29.0(19) 3.2	29.1(3)	28.0(10) 4.4	40.8(3)	32.0(19) 2.2
Blood glucose (Mg./100 cc.)	84.2(12) 10.0	82.0(24) 8.2	74.3(8) 17.0	86.0(17) 10.5	93.7(3)	94.8(9) 12.8	73.4(2)	88.4(16) 9.2
Total cholesterol (Mg./100 cc.)	122.3(13) 44.0	61.6(24) 14.3	133.9(8) 17.8	82.4(12) 8.0	112.4(3)	75.3(10) 6.6	106.8(3)	82.0(12) 18.8
Free cholesterol (%)	27.6(13) 1.1	29.6(24) 3.5	27.9(8) 3.3	29.8(12) 3.0	27.6(3)	35.5(10) 2.6	27.2(2)	33.4(12) 2.9
Prothrombin time (seconds/cc.)	11.6(10) 2.1	13.6(19) 2.8	11.1(7) 0.2	11.7(14) 1.9	11.8(3)	12.2(5)	12.0(3)	10.8(14) 1.9
Fibrinogen (Gm./100 cc.)	0.18(13) .05	0.11(22) .05	0.31(6) .1	0.12(17) .05	0.29(3)	0.14(10) .05	0.33(2)	0.18(16) .07
Hematocrit (%)	47.6(3)	37.8(19) 4.0	38.1(7) 4.6	35.6(25) 2.7	36.9(3)	29.5(12) 4.3	35.4(2)	33.3(20) 3.3

*The figures in parentheses represent the number of determinations carried out. The figure below each mean is the standard deviation calculated according to the following formula: Standard deviation equals the square root of the sum of the measurements multiplied by the square of the deviation from the normal, divided by the number of determinations.

cases there are decreases in total plasma protein, albumin level, albumin globulin ratio, total cholesterol and fibrinogen and a slight decrease in the hematocrit value. The hematocrit reading in the case of dog 39 shows

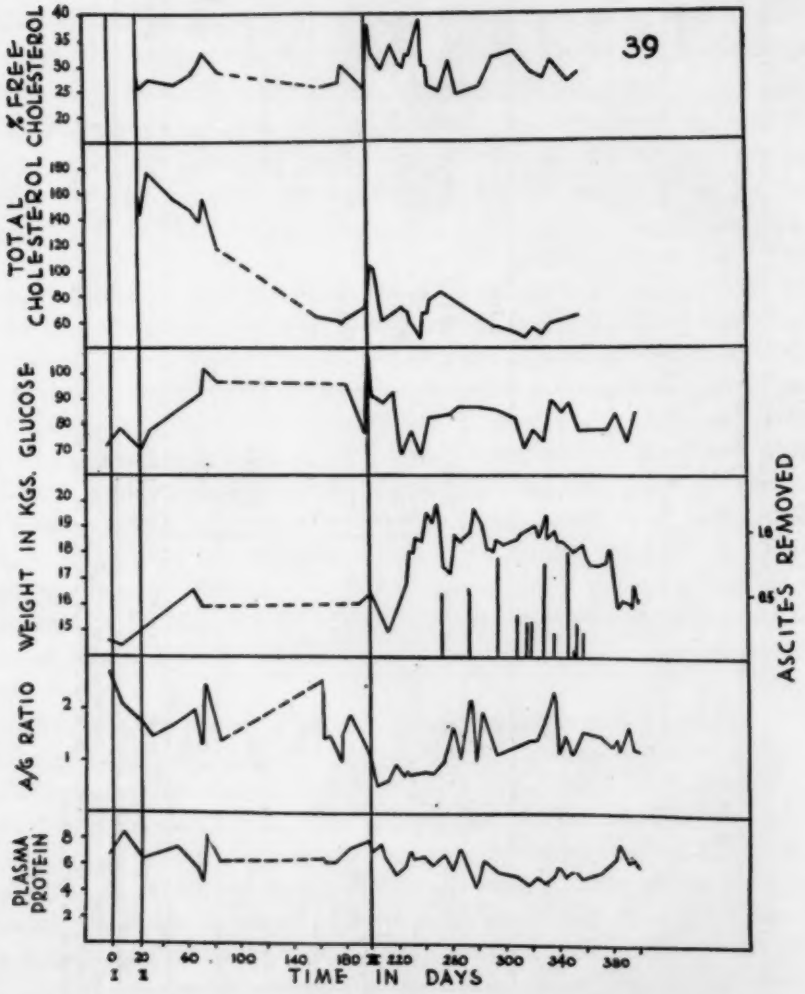

Fig. 1.—Changes in percentage of free cholesterol, total cholesterol (milligrams per hundred cubic centimeters), blood glucose (milligrams per hundred cubic centimeters), weight, ascitic fluid removed (liters), albumin-globulin ratio and total plasma protein (grams per hundred cubic centimeters) prior to and after operative procedures I, II and III for dog 39.

a large decrease, but this is more apparent than real, since the average before operation III was based on only three determinations. Prothrombin clotting time and nonprotein nitrogen and blood glucose levels appear

to be unchanged. The percentage of free cholesterol, on the other hand, rose slightly in all the experimental animals.

For the 2 animals (dogs 39 and 42) on which sufficient data were available to determine the standard deviations before and after operation III, standard errors were calculated and statistical significance ascer-

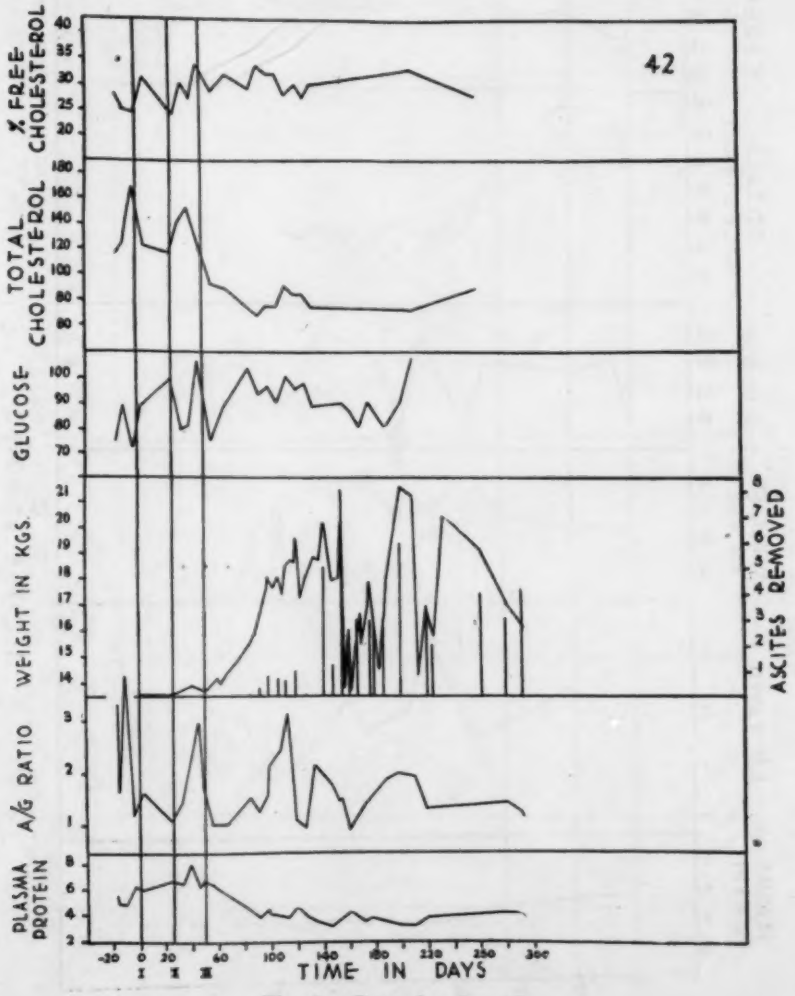

Fig. 2.—Data for dog 42.

tained by dividing the difference between the means by the standard error. A resultant figure of greater than 2 was considered significant and not due to random sampling. With the use of this criterion, significant differences before and after operation III are demonstrated for total plasma protein, albumin levels, fibrinogen and total cholesterol. No sig-

nificant differences are shown for the glucose and nonprotein nitrogen levels or for the hematocrit values. The difference between the means for prothrombin clotting time is not significant for dog 39 but is for dog

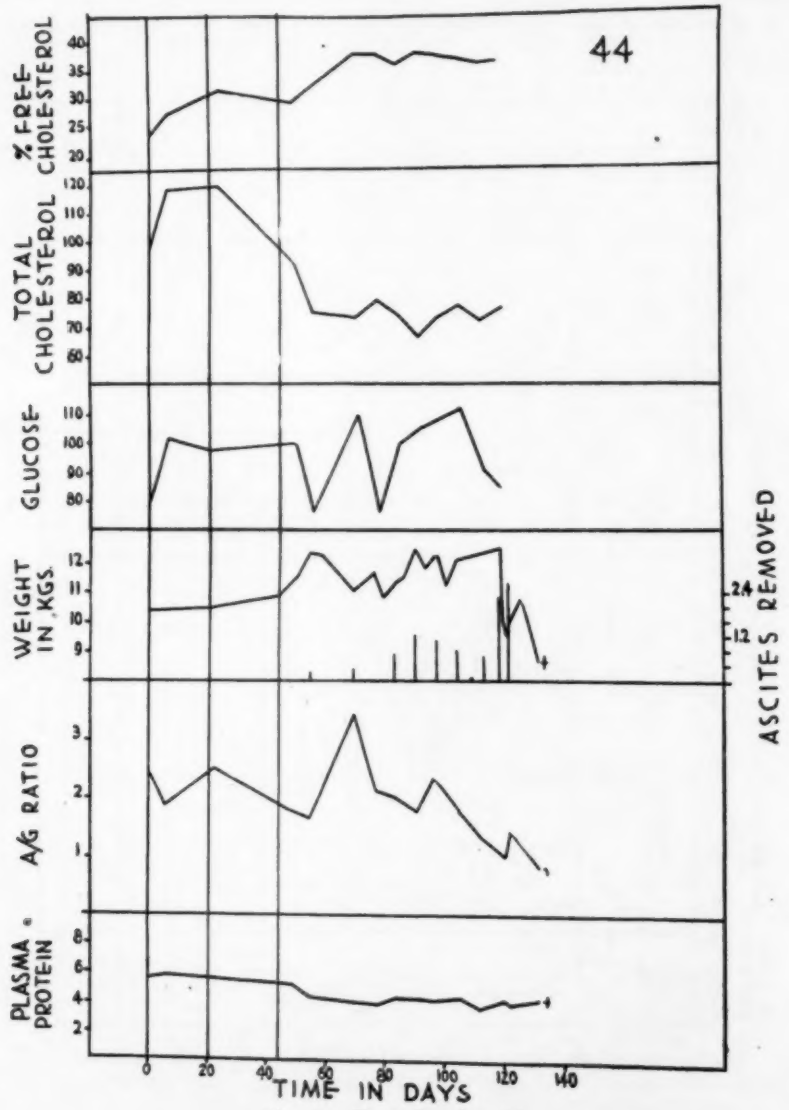

Fig. 3.—Data for dog 44.

42; the difference for the percentage of free cholesterol, on the other hand, is significant for dog 42 but not for dog 39.

It would appear from the foregoing data, if one considers only nonprotein nitrogen, prothrombin clotting time and blood glucose, that no

hepatic damage has occurred. The data on hematocrit readings are interpreted to mean that no hemoconcentration has taken place. On the other hand, if one considers the data on total protein, albumin level, albumin-globulin ratio, total cholesterol and plasma fibrinogen it would appear

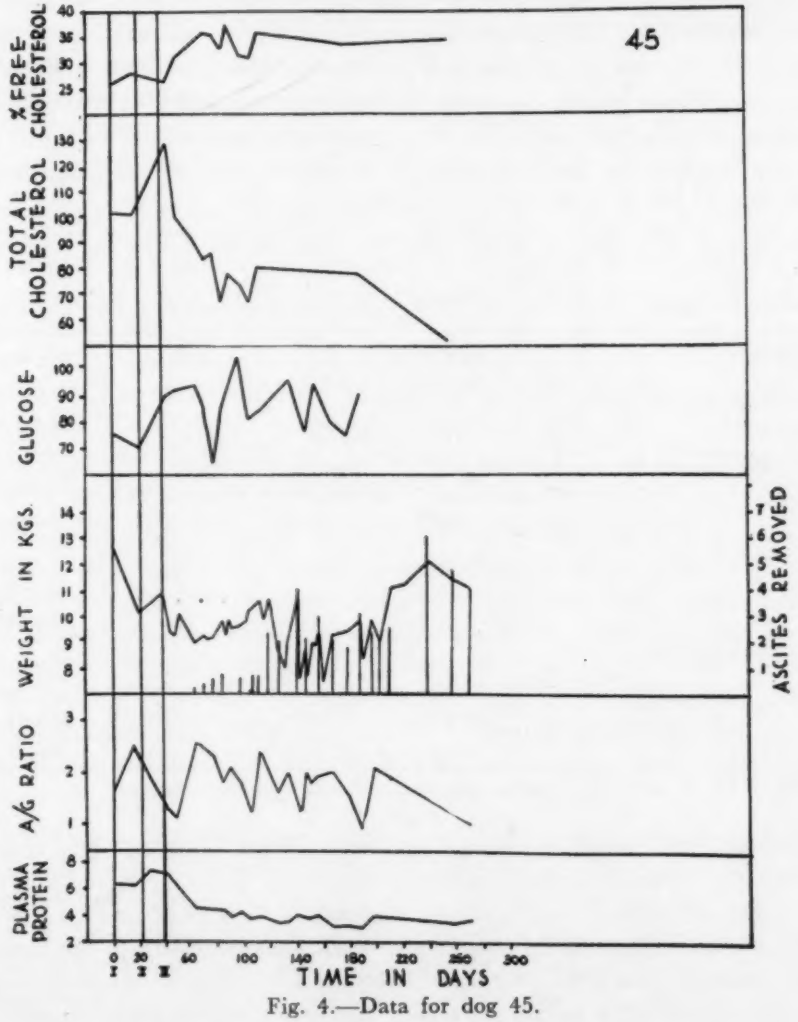

Fig. 4.—Data for dog 45.

that considerable damage has been brought about. A decrease in the albumin and fibrinogen fractions of the plasma is indeed considered to be among the most reliable criteria of hepatic damage, since it is generally agreed[12] that these proteins are produced in the liver. It is also believed

12. Bodansky, M., and Bodansky, O.: Biochemistry of Disease, New York, The Macmillan Company, 1940, p. 234.

that cholesterol is esterified in the liver, so that any marked decrease in the total cholesterol such as is shown here is usually interpreted to indicate damage of the liver.

In the material just presented nothing has been said concerning the composition of the ascitic fluid. Since this fluid is normally not present but accumulates with the increase in pressure in the liver and in the portal veins, any estimate of hepatic function must take into account its composition. If the liver is not really damaged but is forming normal quantities of albumin and fibrinogen, then these substances should be found in the ascitic fluid in amounts sufficient to make up the apparent loss from the blood. The data on the composition of the ascitic fluid are presented in table 2. It should be noted that the total protein found in this fluid

TABLE 2.—*Composition of Ascitic Fluid Withdrawn After Operative Procedure III**

Constituent	Dog 39	Dog 42	Dog 44	Dog 45
Total fluid removed (liters)	5.2	60.2	14.4	41.6
Total protein in fluid (grams)	210	1515	382	971
Total protein (Gm./100 cc.)	5.6(19)	3.8(18)	4.1(11)	3.8(21)
Total albumin (Gm./100 cc.)	3.2(19)	2.4(18)	2.6(11)	2.5(21)
Total globulin (Gm./100 cc.)	2.4(19)	1.4(18)	1.5(11)	1.3(21)
Albumin-globulin ratio	1.3(19)	1.7(18)	1.7(11)	1.9(21)
Total cholesterol (Mg./100 cc.)	45.1(4)	56.7(7)	45.6(4)	49.2(4)
Free cholesterol (%)	10.6(4)	13.0(7)	17.1(5)	13.6(4)

*The figures in parentheses represent the number of determinations carried out.

is considerable; expressed on a basis of grams per hundred cubic centimeters, it is almost as concentrated as that in the blood. It should also be noted that this fluid contains large amounts of cholesterol and on a percentage basis accounts for almost all the cholesterol lost from the blood. Of special interest is the observation that the percentage of free cholesterol is much lower than that in the blood, thus offsetting the apparent rise in the free cholesterol of the plasma. Unfortunately no assays were carried out on the fibrinogen content of the ascitic fluid. Since fibrinogen (m.w. 69,300) is in the size range of albumin (m.w. 70,000), one would expect that it would leave the blood stream under the same conditions as does albumin and would probably be present in the ascitic fluid. The observations would make it appear that hepatic function is indeed not impaired but that the decrease in the constituents noted is due to congestion of

the liver and to subsequent portal hypertension brought about by the partial constriction of the posterior vena cava just anterior to the diaphragm.

One may argue that the concentration of the constituents mentioned in the ascitic fluid is not of importance but rather the absolute quantities. In this connection the following calculations have been carried out from the data obtained on dog 45 (Calculations from the data on other dogs gave similar results.) If the value for the plasma protein is taken as 6.7 Gm. per hundred cubic centimeters, and it is assumed that there are 41 cc. of plasma for every kilogram of body weight,[13] there would be present prior to operation III on the average of 30.22 Gm. of plasma protein in the entire animal. Two months after operation III, when the production of ascitic fluid was considerable, the plasma protein level fell to 4.0 Gm. per hundred cubic centimeters. At this time the weight of the dog was approximately 9 Kg. The total plasma protein would then be 14.76 Gm. In one three day interval there was withdrawn from this animal 3,000 cc. of ascitic fluid which contained 65.1 Gm. of total protein, representing a daily loss in the ascitic fluid of 21.7 Gm. Adding this value to the figure for the plasma protein, one gets a total of 36.46 Gm., as compared with 30.22 Gm. prior to operation III. Thus, when the protein content of the ascitic fluid is taken into account, it appears that the animal has not decreased its protein production; it has only apparently done so, since protein is constantly being lost into the ascitic fluid.

As further indexes of hepatic function, determinations of serum phosphatase activity and sulfobromophthalein clearance tests were carried out. The results are shown in tables 3 and 4. The phosphatase activity in all instances is within normal limits, the values tending to be low rather than high, as might be expected in certain types of hepatic damage. The sulfobromophthalein clearance tests were carried out on 3 dogs after operative procedure III. In only 1 dog (45) are the retention values high.

The data presented here support the thesis that hepatic congestion in the dog with accompanying portal hypertension does not, per se, produce damage of the liver. This is also borne out by histologic examination of the livers of the animals at autopsy. A brief description of the findings for 2 of the dogs, dog 39 and dog 42, is set forth in the following paragraphs. The results of histologic studies in the 2 described represent the extremes. Dog 39 showed the least change and dog 42 the most. These observations are consistent with the chemical changes described.

In dog 39 the liver showed intense and widespread congestion of the sinusoids in the central half of the lobules; occasional areas of small hem-

13. Everett, M. R.: Medical Biochemistry, New York, Paul B. Hoeber, Inc., 1942, p. 526.

orrhage and necrosis of the adjacent hepatic cords were present immediately adjacent to the central vein in some of the congested areas. Aside from these changes, there were no histologic alterations in the cells of the hepatic cord, capillaries or portal spaces.

In the spleen the follicles were fairly well preserved; no secondary follicles were visible. There was moderate sinus hyperplasia, and occasional sinusoids contained acellular albuminoid-like material. There was some diminution in the amount of lymphoid tissue in the red pulp. Occasional recent perifollicular pulp hemorrhage was present. Moderate numbers of megakaryocytes were present within the red pulp.

There was no histologic change in the pancreas or in the kidneys.

Photomicrographs of the liver, spleen, kidney and pancreas from dog 39 are shown in figures 5 to 8.

TABLE 3.—*Phosphatase Activity After Operative Procedure III**

	Dog 39	Dog 42	Dog 44	Dog 45
Average	0.71	0.86	1.02	0.86
Range	0.17 to 1.53	0.19 to 2.3	0.17 to 2.37	0.17 to 2.23
Number of samples	11	15	8	15

*Results expressed as Bodansky units.

TABLE 4.—*Sulfobromophthalein Clearance After Operative Procedure III*

	Dog 39	Dog 44	Dog 45
After 5 minutes	20.5	22.0	53.0
After 15 minutes	1.0	5.0	12.0
After 5 minutes	21.0	30.5	70.0
After 15 minutes	1.0	18.5	22.0

In dog 42 all the sections of the liver showed widespread recent hemorrhage and some necrosis of hepatic cords in and immediately adjacent to the hemorrhagic areas. These hemorrhagic areas involved chiefly the central portion of the lobule and then spread toward the periphery, and only occasionally was there encroachment on the portal spaces. Where the hemorrhage and necrosis rached to the vicinity of the portal spaces there appeared some increase in prominence and width of the fibrous tissue stroma, suggesting collapsed fibrosis, and in such areas there was occasionally present a capillary angiomatous-like congestion of the sinusoids and vessels of the portal spaces; a similar angiomatous-like appearance was present in areas where the hemorrhage involved the neighborhood of sublobular veins. There was no evidence of regeneration

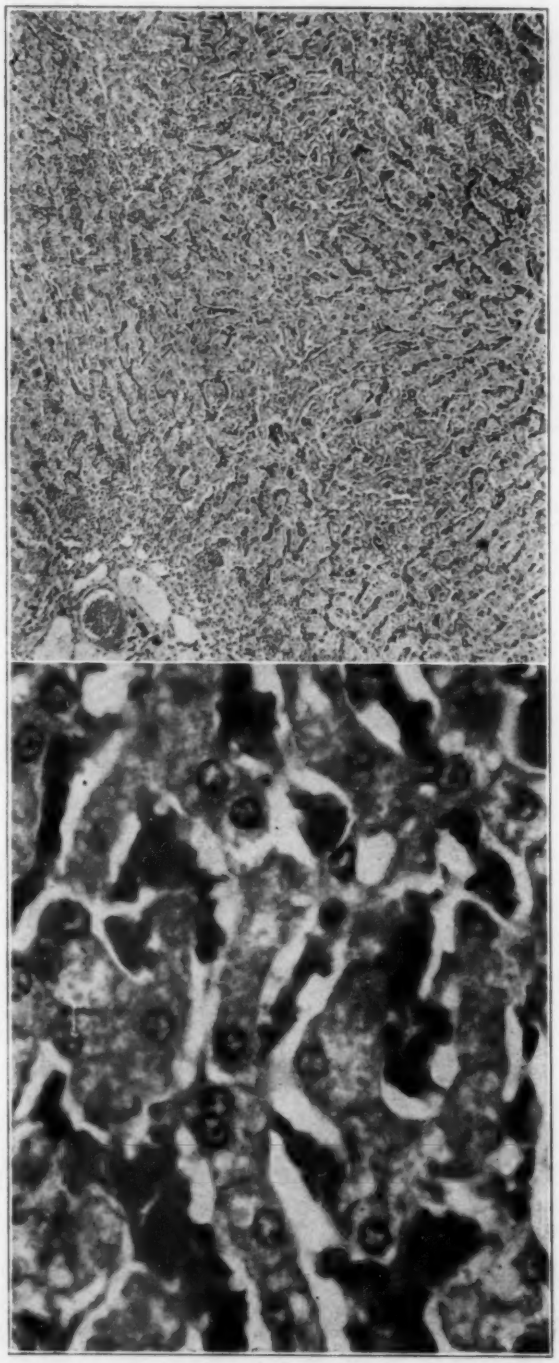

Fig. 5.—Liver from dog 39.

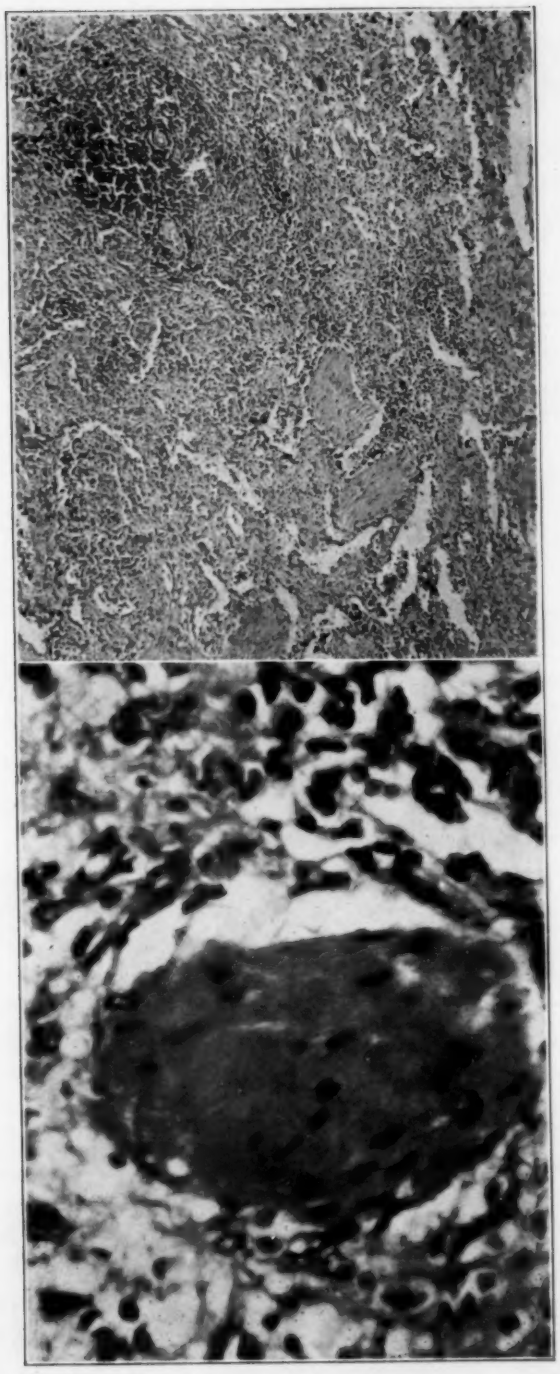

Fig. 6.—Spleen from dog 39.

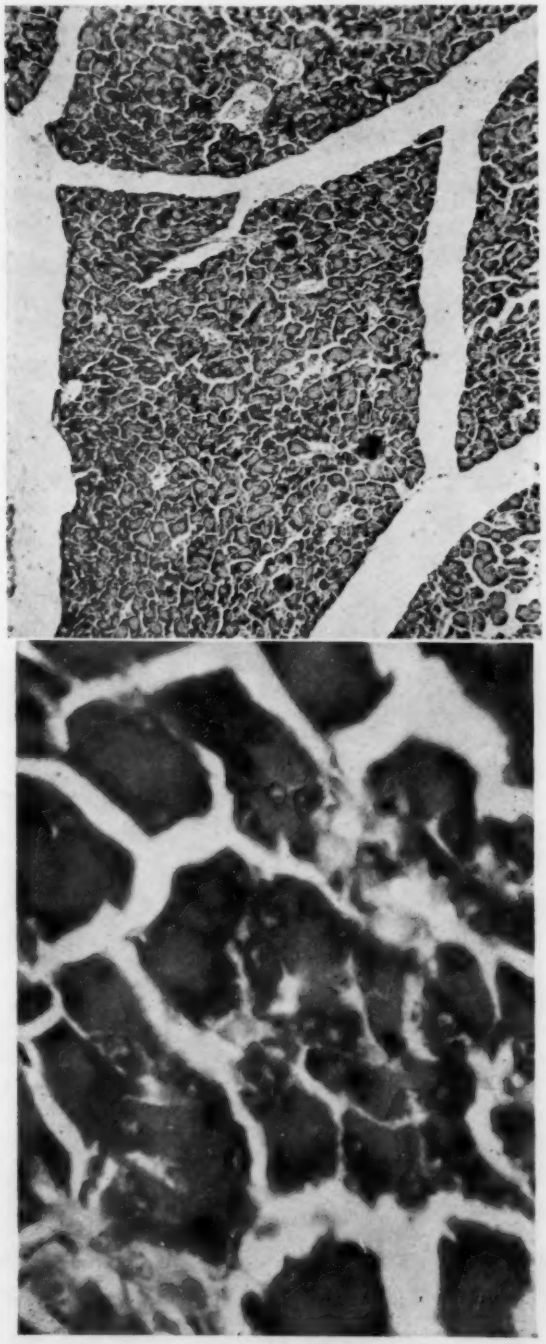

Fig. 7.—Pancreas from dog 39.

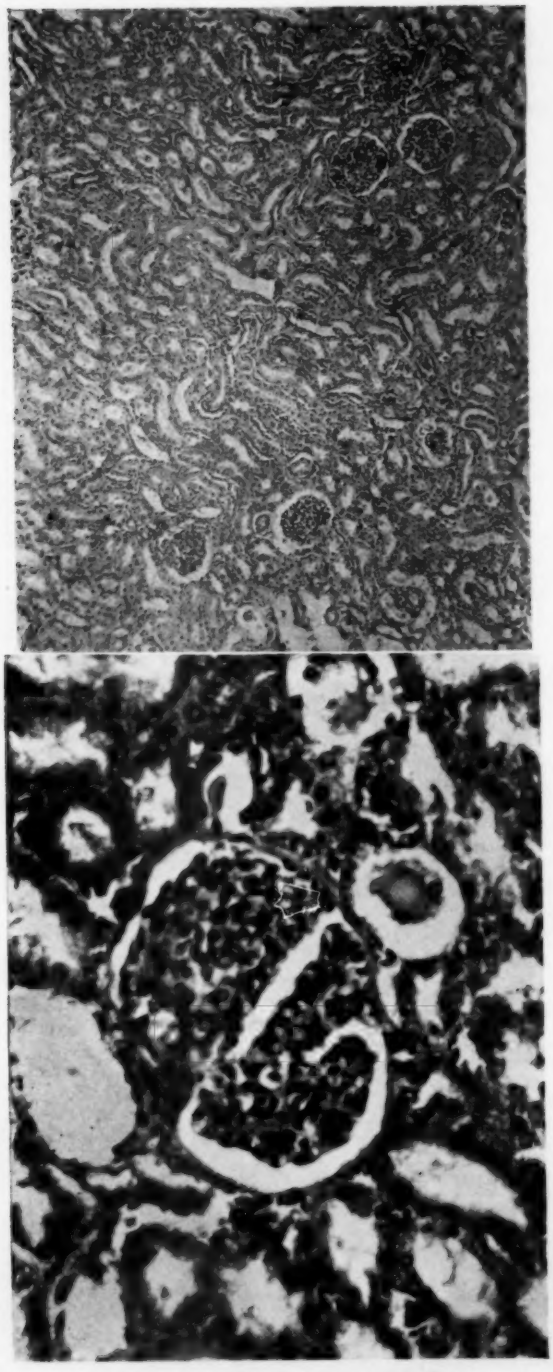

Fig. 8.—Kidney from dog 39.

of cord cells or of Kupffer cell hyperplasia, nor was there any evidence of intrinsic vascular changes.

In the spleen the follicles were completely absent, and the red pulp revealed considerable lymphocytic exhaustion and was composed of loose fibrosis and a cellular reticulum in which a slight sinus hyperplasia, moderate pulp congestion and occasional small hemorrhages of recent character were present. These changes were widespread. Here and there were scattered a few small masses of hemosiderin-like pigment, chiefly within phagocytic cells. The trabeculae were prominent but not cellular, and there were no vascular changes.

In the pancreas there were no abnormal histologic changes, and, with the exception of an extremely slight and highly questionable swelling, opacity and occasional coarse granularity in the epithelium of the convoluted tubules, there were no histologic changes in the kidneys.

Photomicrographs of the liver, spleen, kidney and pancreas from dog 42 are shown in figures 9 to 12.

COMMENT

It is concluded on the basis of the chemical and histologic observations described that the complete severing of the posterior vena cava cauded to the liver (in two stages) followed by the partial occlusion of the posterior vena cava just anterior to the diaphragm produces hepatic congestion and accompanying portal hypertension but no significant hepatic damage in the dog. Large amounts of ascitic fluid accumulates in some instances, which is due primarily to the increased pressure in the liver and in the portal veins, but hepatic function, as measured by studies of a whole series of constituents of the blood believed to be intimately associated with normal activity of the liver, is not interfered with. Changes in the blood do occur in some instances, but these can be explained by taking into account the composition of the ascitic fluid.

In the description of the results, no attempt has been made to correlate the findings with those presented elsewhere in the literature. The literature on the clinical pathology and the function of the liver is so extensive that it is difficult to present only part of the picture without presenting the picture in its entirety. This has been adequately done in the many reviews which have appeared on the subject. It is for this reason

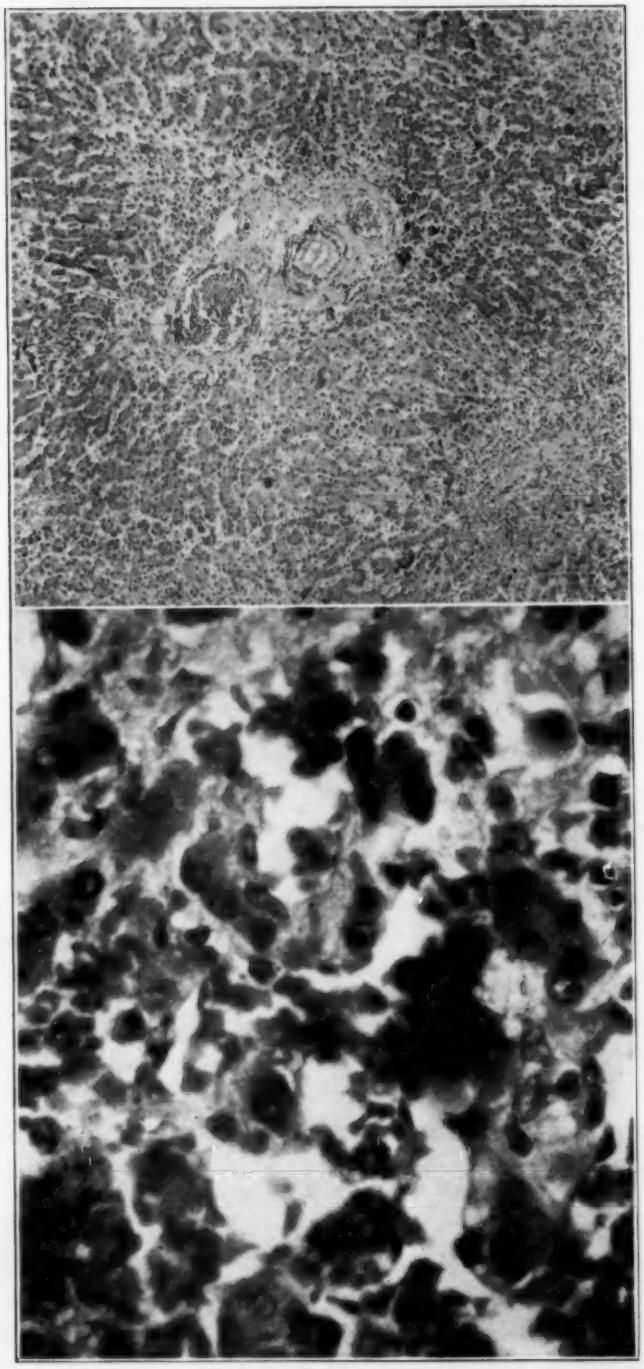

Fig. 9.—Liver from dog 42.

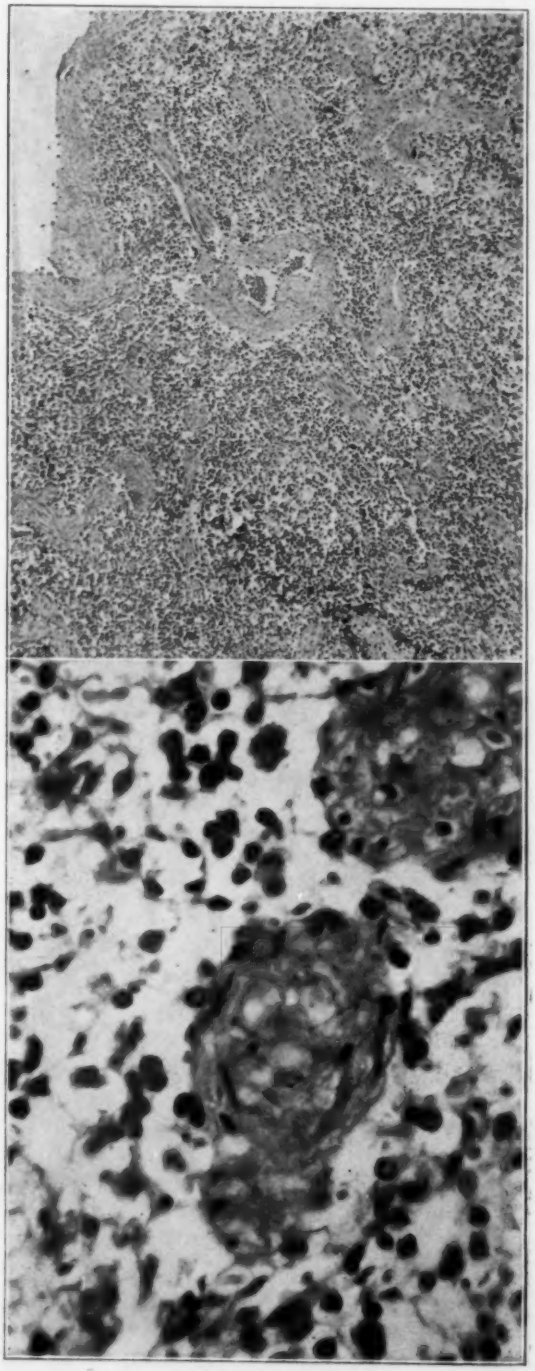

Fig. 10.—Spleen from dog 42.

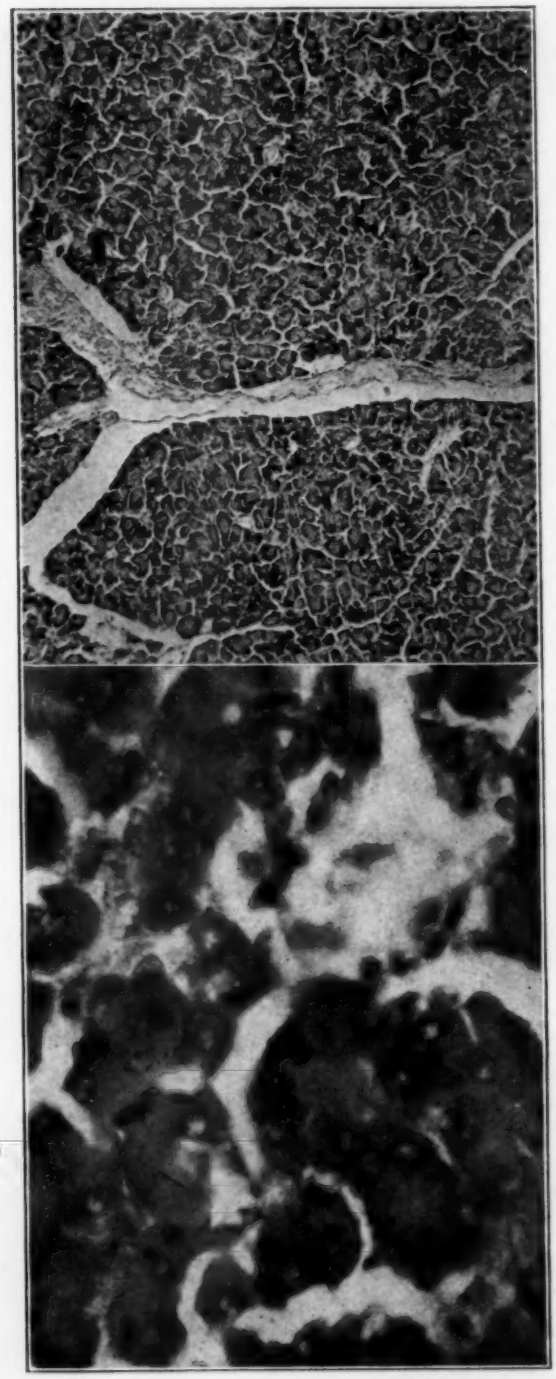

Fig. 11.—Pancreas from dog 42.

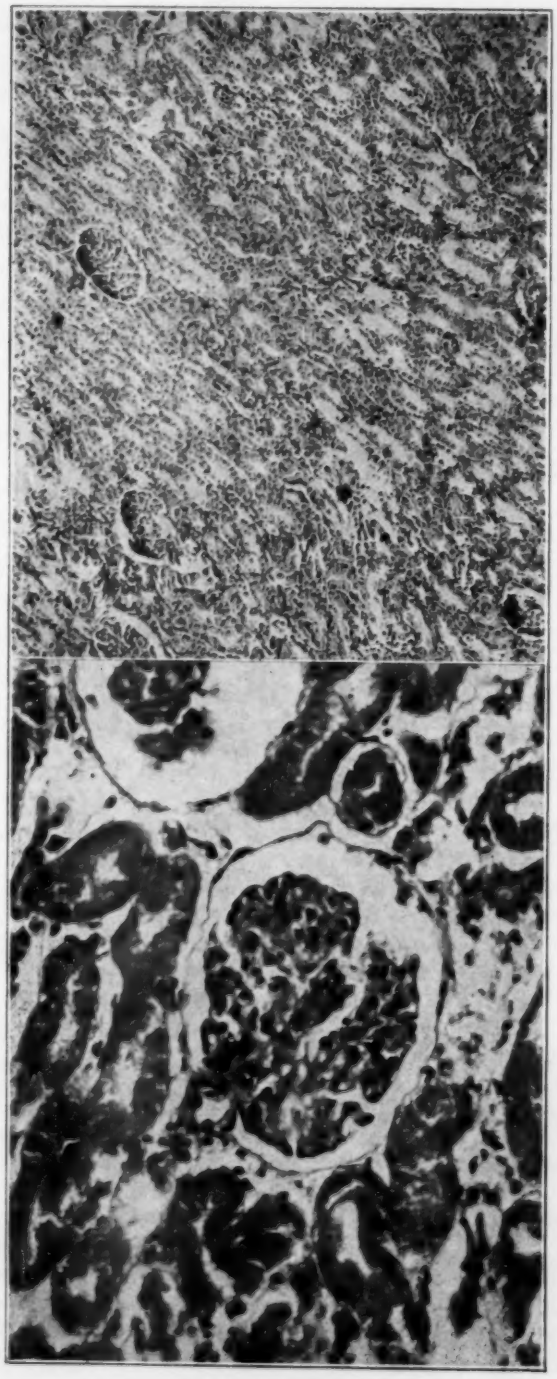

Fig. 12.—Kidney from dog 42.

that the present paper has been restricted to a short description of the results obtained under the particular conditions of the operative procedures set forth in a preceding paper.[1]

SUMMARY

Congestion of the liver and accompanying portal hypertension, produced by a three stage operative procedure previously described, do not result in hepatic damage in spite of the fact that large amounts of ascitic fluid are produced. This conclusion is borne out by chemical studies of constituents dependent on blood hepatic function and by histologic examination of the liver, spleen, pancreas and kidney at autopsy.

1. Kershner, D.; Hooton, T. C., and Shearer, E. M.: The Production of Experimental Portal Hypertension in the Dog; Anatomy of Hepatic Veins in Dog, Arch. Surg. **53**:425 (Oct.) 1946.

RELAXATION OF THE GASTRIC MUCOSA PRODUCING PYLORIC OBSTRUCTION

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COPENHAGEN

THE MUCOUS membrane in the pyloric region of the stomach may prolapse through the pylorus and thereby cause gastric pains and vomiting. Such a prolapse of the gastric mucosa is generally due to the presence of a stalky tumor, but in rare cases it is caused exclusively by an abnormal redundance and laxness of the mucous membrane in the pyloric region of the stomach.

Schmieden[1] seems to have been the first to describe a case of this kind. The patient was a woman, aged 27, with dyspeptic symptoms. At operation on the pyloric region of the stomach, he found a transverse fold of mucous membrane, which he thought could shut off the access to the pylorus in the manner of a valve. More recently cases have been reported by Eliason, Pendergrass and Wright,[2] Meyer and Singer,[3] Pendergrass and Andrews,[4] Rees,[5] Bohrer and Copleman,[6] and Norgore and Shuler.[7]

This condition seems to be of fairly rare occurrence, to judge by the reports in the literature. Norgore and Shuler (1945) stated that there are

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From the Surgical Department A of the Bispebjerg Hospital (Surgeon-in-Chief, Jens Foged, M.D.).

1. Schmieden, V.: Die Differentialdiagnose zwischen Magengeschwür und Magenkrebs; die pathologische Antaomie dieser Erkrankungen in Beziehung zu ihrer Darstellung in Röntgenbilde, Arch. f. klin. Chir. **96**:253, 1911.

2. Eliason, E. L.; Pendergrass, E. P., and Wright, V. W. M.: Roentgen-Ray Diagnosis of Pedunculated Growths and Gastric Mucosa Prolapsing Through Pylorus: Review of Literature, Am. J. Roentgenol. **15**:295, 1926.

3. Meyer, K. A., and Singer, H. A.: Intermittent Gastric Ileus Due to Mechanical Causes, Surg., Gynec. & Obst. **53**:742, 1931.

4. Pendergrass, E. P., and Andrews, J. R.: Prolapsing Lesions of Gastric Mucosa, Am. J. Roentgenol. **34**:337, 1935.

5. Rees, C. E.: Prolapse of Gastric Mucosa Through Pylorus: Surgical Treatment, Surg., Gynec. & Obst. **64**:689, 1937.

6. Bohrer, J. V., and Copleman, B.: Prolapsing Redundant Gastric Mucosa: Case Report, Radiology **31**:220, 1938.

7. Norgore, M., and Shuler, I. J. D.: Extrusion of Gastric Mucosa Through Pylorus: Report on Two Patients Treated by Partial Gastrectomy, Surgery **18**:452, 1945.

found descriptions of 23 cases only (their own 2 cases included) in which the diagnosis was verified by operation. Cases are, however, presumably more common than it is generally supposed, and the abnormality will probably be diagnosed more often as it becomes better known.

The symptoms consist of intermittent, cramplike pains in the epigastrium. The pains can be brought on by ingestion of food or, as in 1 of the cases here reported, by bodily exertion. They may be accompanied with vomiting, which lessens or entirely eliminates them. The disease may, if it persists for an appreciable length of time, cause a rather considerable loss of weight.

Fig. 1.—Roentgenogram demonstrating pyloric occlusion.

The case histories of 2 patients with this abnormality are given here.

REPORT OF CASES

Case 1.[8]—A waiter, aged 52, was transferred from the medical department to be operated on for pyloric stenosis. He had previously been in good health, but for the past three years he had been suffering from intermittent cramplike pains in the epigastrium radiating into the back. The pains would generally come on in connection with his meals, but they could also be brought about by bodily exertion. Occasionally they were accompanied with profuse, acid, watery vomiting, which brought relief. Eating brought no relief. The patient had lost 7 Kg. in weight in the course of the nine months before his admission to the hospital.

8. Reported to the Danish Surgical Society on April 14, 1946; Nord. med. **32**:2334 (Oct. 11) 1946.

In addition to these symptoms there were moderate constipation and some disposition to meteorism. He admitted that his daily consumption of alcohol and tobacco was great and that he lived, on the whole, an irregular life. The ordinary physical examination revealed nothing abnormal.

Of the results of other examinations, the following may be mentioned: The reaction to a benzidine test of the feces was 1 plus on one occasion and 2 plus on another, and on two other occasions it was negative. After an Ewald test meal the

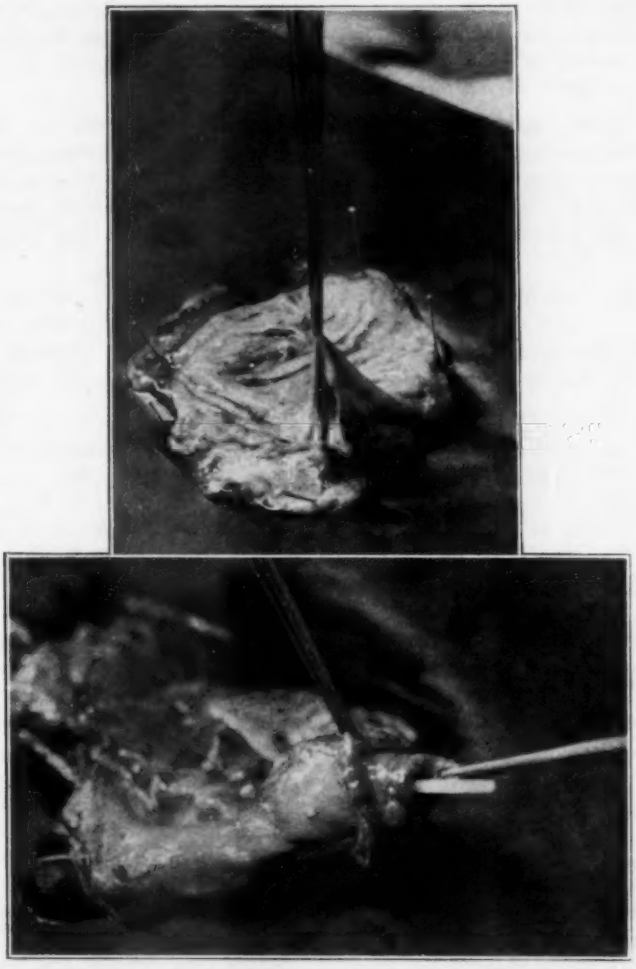

Fig. 2.—Redundant gastric mucous membrane.

free acid, determined with congo red, was 35 cc. and the combined acid, determined with phenolphthalein, 47 cc. The volumes were 14 and 81 cc. Kemp's test showed traces of retention after six hours. The Wassermann reaction was negative, and the sedimentation rate was 3 mm. in one hour. The urine contained no albumin, sugar or pus. The blood pressure was 125 systolic and 65 diastolic. Roentgenologic and electrocardiographic examination of the heart revealed nothing abnormal.

Roentgenologic Examination of the Stomach.—All the roentgenograms demonstrated the same uniformly shaped termination of the contrast medium in the pyloric area. The medium passed slowly into the small intestine. A distinct bulb was not seen in any of the roentgenograms. A little contrast was still visible in the stomach four hours after the administration. The diagnosis was pyloric stenosis caused by a tumor (fig. 1).

Operation.—At operation the stomach was found to be slightly dilated and hypertrophic, but the surface was normal. A tumor-like formation, the size of the end of a thumb, was palpable in the pyloric region. This formation could be pushed from side to side in the lumen. Resection of the stomach was done according to Billroth's second method.

The excised part of the stomach contained neither tumors nor ulcerations. However, the gastric mucous membrane was exceedingly redundant and so loosely attached in the pyloric region of the stomach that it could be lifted up in a 2 cm. high transverse fold, which could be drawn 1 cm. down through the closed pylorus (fig. 2). The pyloric musculature was greatly hypertrophic and almost 1 cm. thick.

The postoperative course was uneventful. Two years after the operation the patient has reported that he is completely free from symptoms in spite of the fact that he is by no means careful of himself or of his stomach. Overfilling of the stomach may occasionally give rise to a slightly oppressive sensation in the epigastrium.

Case 2.—A janitor, aged 62, had for ten years or so an oppressive sensation in the epigastrium after large meals. For the twelve months before his admission to the hospital he had had attacks of violent cramplike pains as well, which at first were limited to the epigastrium but which gradually spread to the entire abdomen. The attacks of pain could be brought about by bodily exertion and were sometimes accompanied with vomiting, which immediately relieved them. He therefore often tried to provoke vomiting by passing a finger down the gullet. He had lost 25 Kg. in weight in the course of the last six months before his admission. In addition to these symptoms there was found only slight constipation. The ordinary clinical examination revealed nothing abnormal except that the patient was somewhat emaciated. The results of other examinations were as follows: The reaction to a benzidine test of the feces was 1 plus on one occasion and negative on three occasions. After an Ewald test meal the congo red test revealed no free acid and the phenolphthalein test 25 cc. of combined acid. The volumes were 63 and 12 cc. Kemp's test showed no retention in six hours. The sedimentation rate was 30 mm. in one hour, and the reaction to Takata's test was negative.. The blood pressure was 120 systolic and 80 diastolic. Roentgenologic examination of the heart and the colon showed nothing abnormal. The electrocardiogram was normal.

Roentgenologic examination of the stomach showed irregularities in the filling of the prepyloric region by the contrast medium which aroused suspicion of a polypous tumor formation.

Operation was done on the assumption that gastric cancer was present, but the stomach proved to be of normal appearance, with no signs of ulcer or tumor. However, an almond-sized, polypus-like intumescence was palpable in the prepyloric region. This could be pushed from side to side in the lumen. When the stomach was opened, the intumescence proved to consist of a projecting fold of the mucous membrane which could be drawn right down through the pylorus.

Resection of the stomach was done according to Billroth's first method. Examination of the remaining part of the abdomen revealed nothing abnormal.

The excised part of the stomach contained no tumors. However, the gastric mucosa in the prepyloric region was extremely redundant and so loosely attached that it formed a considerable transverse fold which could be drawn some way down past the pylorus. In addition the pyloric musculature was found to be hypertrophic.

The postoperative course was uncomplicated except for a retracted gastric retention. The patient's symptoms disappeared after the operation, but he has so far been under observation for one month only.

COMMENT

The abnormal laxness and redundance of the gastric mucosa must be regarded as the pathologicoanatomic basis for this disease. I have, therefore, preferred to use the term "relaxation of the gastric mucosa," unlike earlier writers, who have used designations referring to the prolapse of the gastric mucosa. Indeed, the symptoms develop generally on account of prolapse of the mucous membrane, however, such a prolapse is far more frequently due to the presence of polypous tumors, which in the literature are still mixed up with the abnormality described in this paper. Besides, the symptoms need not necessarily be brought about by a prolapse of the mucous membrane but may be the result of the mucous membrane shutting off the access to the pylorus like a valve (Schmieden). It therefore seems to me most expedient to use a term which covers the primary anatomic abnormality.

The prolapsed folds of mucous membrane sometimes present chronic inflammation and hypertrophy, which some writers regard as the primary cause of the prolapse. The changes can, however, just as well be regarded as a consequence of the frequent incarcerations in the pylorus.

The attending hypertrophy of the pylorus is no doubt due to the increased work of drawing the gastric mucosa down into the duodenum. The mucous membrane is loosened still more and is more easily caught by the peristalsis. Thus a vicious circle develops, which can give rise to attacks increasing in frequency and in severity.

The treatment consists in most cases in excision of the projecting fold of mucous membrane, generally with a favorable result. Norgore and Shuler performed resection on both their patients, in one instance on account of a concurrent ulcer. Resection must be the rational solution in cases in which the mucous membrane is loosely attached over a greater area.

SUMMARY

A description is given of an abnormality of the gastric mucosa which consists in the mucous membrane being exceedingly redundant and loosely attached in the pyloric region.

The case histories of 2 patients with this abnormality are reported. Both patients suffered from increasing attacks of severe cramplike pains in the epigastrium, occasionally accompanied with vomiting, which relieved the pain, and with loss of weight.

The roentgenologic appearance of the stomach argued in both cases for the presence of a tumor.

At operation a tumor-like formation was palpable in the pyloric region of the stomach in both patients. This formation later proved to be a large fold of the lax gastric mucosa which could be drawn through the pylorus down into the duodenum. In addition the pyloric musculature was found to be hypertrophic.

The clinical signs can be explained as being due to the fact that the peristalsis draws the gastric mucosa down through the pylorus, which is thereby obstructed.

The treatment consisted in resection of the pyloric region of the stomach. None of the patients have had attacks since the operation.

CHRONIC PANCREATITIS CAUSING COMPLETE AND INCOMPLETE OBSTRUCTION OF THE COMMON BILE DUCT

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AND
ALBERT BEHREND, M.D.
PHILADELPHIA

CHRONIC pancreatitis is a relatively uncommon disease. It is often extremely difficult to distinguish between it and carcinoma involving the pancreas. When the diagnosis is doubtful, biopsy is performed. When the diagnosis of chronic pancreatitis is established, an antastomosis between the biliary system and the stomach, duodenum or jejunum should be done.

REVIEW OF THE LITERATURE

There is a dearth of papers on the subject of obstruction of the common duct due to chronic pancreatitis. It is an entity long known to exist. One of the earliest papers on the subject was that of Riedel,[1] who associated obstructive jaundice with chronic pancreatitis. The similarity between this condition and carcinoma of the head of the pancreas was observed by Mayo-Robson[2] in 1900 and again in 1907.

In 1927 Verhoogen[3] showed that the common duct may be a thread-like structure. This is not always the rule, because he reported that the caliber of the duct may be normal, with no dilatation present. His patients, however, had all the symptoms of choledocholithiasis with jaundice. No stones were found, but the head of the pancreas was indurated. He presented 4 cases. He found no complete obstruction, but simple drainage of the common duct seemed to cure the condition.

Berard and Malley-Guy[4] collected 190 cases of chronic inflammation of the head of the pancreas up to 1930. They operated on 10 patients and

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Read in a Symposium on The Pancreas before the Section on Gastro-Enterology and Proctology at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1947.

1. Riedel, B., cited by Peterson and Cole[5].
2. Mayo-Robson, A. W., cited by Peterson and Cole[5].
3. Verhoogen, J., cited by Berard and Mallet-Guy[4].
4. Berard, L., and Malley-Guy, P.: Du déterminisme de l'ictère dans des pancréatitis chroniques, Rév. med.-chir. d. mal. du foie 7:417-446 (Nov.-Dec.) 1932.

observed the great diversity of the pathologic changes in this syndrome. In all cases obstruction was due to compression by the swollen pancreas.

Carter in 1935 reported a case in which symptoms had been present for only five weeks before operation. This is not unusual. The patient died of pneumonia. At autopsy the pancreas was replaced by fibrous tissue, with pronounced narrowing of the lumen of the common duct.

Peterson and Cole[5] advised various types of anastomoses, including a Roux procedure, to prevent the regurgitation of food. The proximal stump of the common duct may be anastomosed to the duodenum. In 3 cases reported by them jaundice disappeared.

Carter and Hotz[6] reported 6 cases of 47 in which chronic pancreatitis was present with a normal gallbladder but with obstruction of the common duct; in 3 cases the diagnosis of carcinoma was made, in 2 of which it was disproved by biopsy and in another by autopsy. The patients were all treated by means of cholecystogastrostomy. This operation was successful in 5 of 6 cases. The authors laid stress on the fact that a careful diagnosis is important. This can be accomplished by means of a biopsy.

Heyd and Hotz[7] stated that chronic pancreatitis is the second largest cause of obstruction to the common duct. In their cases they found a dilated common duct with no other evidence of obstruction. They advocated early operation to reduce the operative mortality rate.

Bisgard[8], in a review of some of the literature on this subject, reported 2 of his own cases in which the common duct was obstructed by pancreatitis. The common and hepatic ducts were both dilated. The gallbladder was contracted and contained no stones. Curiously enough, the blood amylase level was elevated. One patient was well for three years; the other died seven months after operation from acute hepatitis.

Whipple[9] reported 2 cases in which total pancreatectomy was performed and 3 others in which a large part of the pancreas was removed for severe pain. The patients had calcareous deposits in addition to pancreatic fibrosis. Jaundice was absent in the majority of cases. There was 1 death in this series.

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5. Peterson, L. W., and Cole, W. H.: Chronic Sclerosing Pancreatitis Causing Complete Stenosis of the Common Bile Duct, Arch. Surg. **51**:15-21 (July-Aug.) 1945.

6. Carter, R. F., and Hotz, R.: Pancreatitis and Biliary Tract Disease, Am. J. Surg. **44**:719-722 (June) 1939.

7. Heyd, C. G., and Hotz, R.: Surgery of the Common Duct, Am. J. Surg. **44**:712-718 (June) 1939.

8. Bisgard, J. D.: Pancreatitis as a Cause of Complete Obstruction of the Common Duct, Ann. Surg. **124**:1009-1017 (Dec.) 1946.

9. Whipple, A. O.: Recent Advances in Surgery of the Pancreas, Pennsylvania M. J. **39**:473-478 (April) 1936.

ETIOLOGIC FACTORS

It has long been our feeling that congenital fibrocystic disease of the pancreas of infants may be a forerunner of chronic pancreatitis. This may be especially true in cases in which chronic pancreatitis develops at or near puberty (Wiglesworth).[10] Bockus[11] supported this contention.

He also referred to Deaver's[12] observation that chronic interlobular pancreatitis may be due to infection from the biliary tract through the lymphatic system. Ascending infection from the duodenum, stricture and stones in the biliary tract are thought to be inciting factors, but it happens that in our cases stones in the gallbladder or in the common duct were found only once.

SYMPTOMS AND DIAGNOSIS

The interpretation of symptoms referable to the pancreas has always been perplexing. The pain and tenderness which accompany chronic pancreatitis are usually intermittent and are hard to distinguish from those accompanying gallbladder colic. In some cases pain is slight or absent and jaundice may be the symptom which causes the patient to seek aid.

Indigestion may precede or accompany attacks of pain. It may follow meals without there having been an indiscretion in diet, but it must be remembered that such indiscretions may precipitate an attack. Jaundice nearly always accompanies or follows the exacerbations, although it may be entirely absent. Whipple[13] and one of us (M.B.)[14] have called attention to this fact. Jaundice may be intermittent. It is usually less severe than that caused by a stone in the common duct or by cancer of the pancreas. When jaundice is the result of complete obstruction of the common duct due to chronic pancreatitis, it is intense and may simulate that which is found after complete obstruction due to cancer of the pancreas. Physical examination of the abdomen is often of little assistance. Dysfunction of the pancreas as reflected by diabetes mellitus or by the finding of undigested food particles in the feces may aid in the preoperative diagnosis. The diagnosis of chronic pancreatitis is usually established only at the time of operation, and values for the serum amylase level, which is ele-

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10. Wiglesworth, R. W.: Fibrocystic Disease of the Pancreas, Am. J. M. Sc. **212**:351-365 (Sept.) 1946.

11. Bockus, H. L., and others: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1946.

12. Deaver, J. B., cited by Bockus and others.

13. Whipple, A. O.: Radical Surgery for Certain Cases of Pancreatic Fibrosis Associated with Calcareous Deposits, Ann. Surg. **124**:991-1008 (Dec.) 1946.

14. Behrend, M.: Diseases of the Gall Bladder and Allied Structures, Philadelphia, F. A. Davis Company, 1947; A Modified Whipple Operation for Carcinoma at the Ampulla of Vater, Am. J. Surg. **72**:599-603 (Oct.) 1946.

vated in attacks of acute pancreatitis, are commonly normal in chronic pancreatitis. A diagnostic aid which is of positive value is the roentgenogram of the abdomen, but this is only so when chronic pancreatitis is accompanied with calcareous deposits.

TREATMENT

Operation is warranted in the presence of intermittent or persistent jaundice whether it is accompanied with pain or not. When there are no

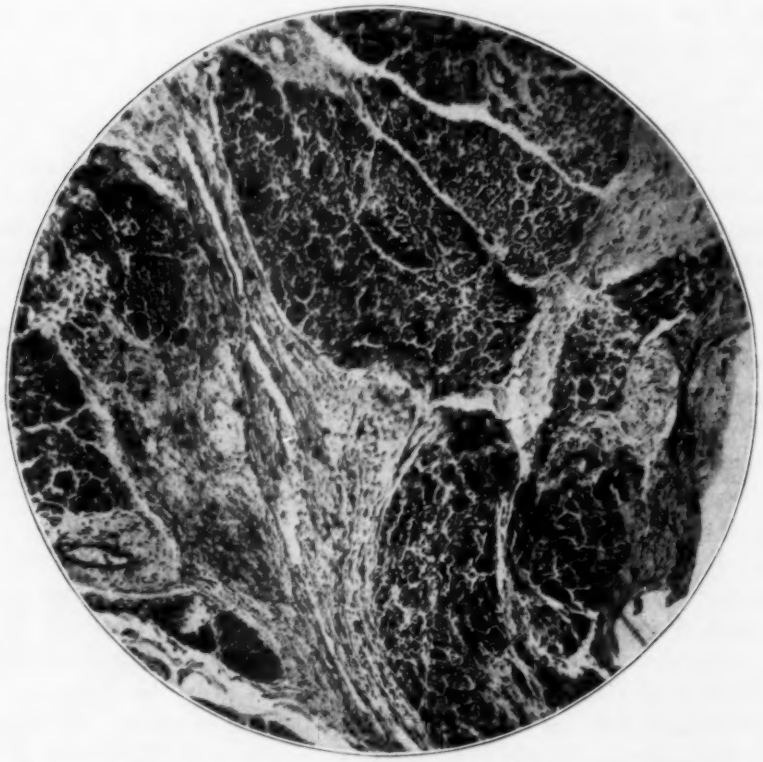

Fig. 1.—Chronic pancreatitis. Pancreatic lobules surrounded by fibrous tissue; × 100.

stones in the gallbladder, suspicion must be centered on the pancreas as the origin of the pain. While there seems to be little difficulty for the surgeon in differentiating the soft pancreas from the hard one, it requires considerable experience to differentiate between the various gradations of hardness to which the pancreas is subject. In all operations on the bile passageways one should never fail to palpate the pancreas. Often chronic pancreatitis may simulate the gross pathologic picture of cancer of the pancreas (figs. 1 and 2). Many authors, including Whipple,

Peterson and Cole, Bisgard, Graham and Mackey[15] and others, have confirmed these observations. So that fewer mistakes may occur, a specimen of the pancreas should be taken for biopsy in all cases in which there is doubt as to the diagnosis. When a hard pancreas is present at operation and no metastasis is found, the possibility of chronic pancreatitis must always be borne in mind.

TYPE OF OPERATION

In the early part of this century, before the technic of anastomosis of the bile passageways with the hollow viscera was well established, the

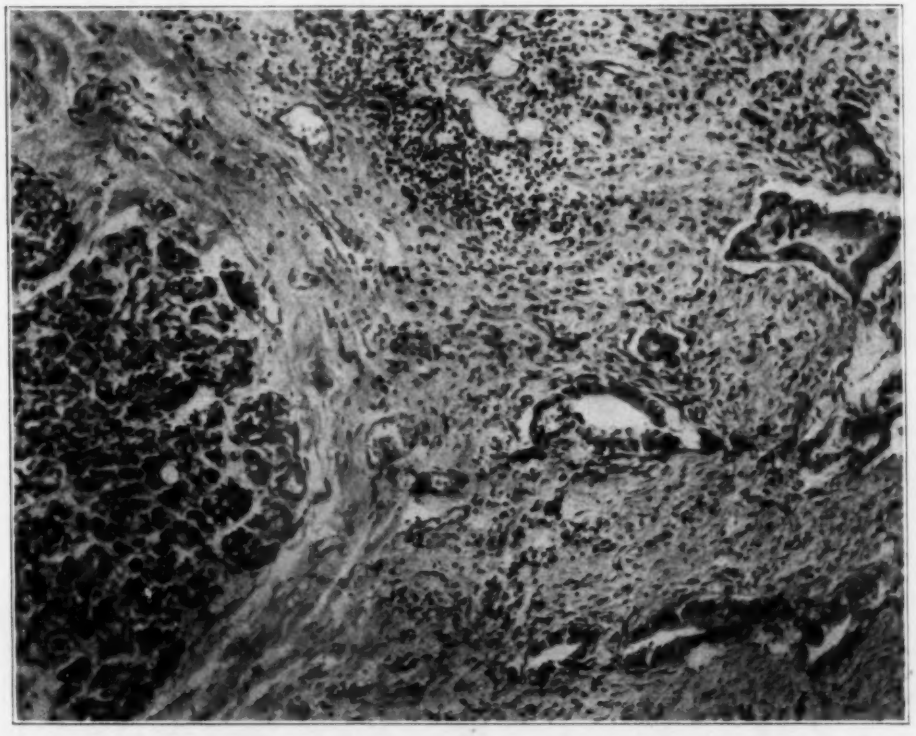

Fig. 2.—Primary adenocarcinoma of the pancreas; × 80.

operation commonly performed was choledochostomy, with the insertion of a T tube. As a matter of fact, Bisgard recently reported the use of the T tube in 2 cases. This affords temporary relief, whereas permanent alleviation of symptoms can be obtained by one of the several types of anastomosis now performed between the gallbladder or the common duct and the gastrointestinal tract. If obstruction of the common duct is complete,

15. Graham, E. A., and Mackey, A. W.: A Consideration of the Stoneless Gall Bladder, J. A. M. A. **103**:1497-1499 (Nov. 17) 1934.

TABLE 1.–*Data on Ten Patients Operated on for Chronic Pancreatitis*

Patient	Age	Date of Admission	Date of Discharge	Symptoms	Operation	Diagnosis at Operation	Compli-cations	Result	Biopsy	Stones	Follow-Up
H. H.	59	5/19/18	6/23/18	Jaundice for 2 weeks	Choledo-chostomy and tube drainage	Chronic pancrea-titis	None	Improved	None	None	None
J. B.	47	10/17/25	11/15/25	Pain, vomit-ing, nausea, jaundice	Cholecysto-duodenos-tomy	Cancer of pancreas or of papilla of Vater; pan-creas hard	None	Cured, lived 20 years; died of coro-nary thrombosis	None	None	Perfectly well until sudden death in February 1947
N. B.	34	2/25/27	3/13/27	Sharp pain, jaundice	Cholecysto-duodenos-tomy	Chronic pancreatitis, hard pancreas	None	Cured	None	From gall-bladder	Perfectly well, accord-ing to report of family physician
A. H.	51	11/ 1/28	12/ 4/28	Pain, nausea, vomiting and jaundice	Cholecysto-duodenos-tomy	Hard pancreas; no nodules	None	Cured	None	None	Perfectly well accord-ing to report of her bro-ther, Dr. Andrussier
S. B.	45	3/ 7/33	4/ 8/33	Severe epi-gastric pain; no jaundice	Cholecysto-duodenos-tomy	Nodular head and body of pancreas	None	Cured	None	None	Perfectly well, accord-ing to report of family physician
K. G.	60	2/ 6/38	2/27/38	Nausea and vomiting; sick 2 years; no jaundice	Cholecysto-duodenos-tomy	Extremely hard pancreas	None	Cured	None	None	Perfectly well, accord-ing to report from patient and family physician
A. B.	49	3/ 6/40	3/20/40	Pain in the right upper quandrant; jaundice present	Cholecysto-gastrostomy	Pancreas extremely hard	None	Cured	None	None	Perfectly well, accord-ing to report from patient and family physician

TABLE 1.—*Data on Ten Patients Operated on for Chronic Pancreatitis—(Continued)*

Patient	Age	Date of Admission	Date of Discharge	Symptoms	Operation	Diagnosis at Operation	Compli-cations	Result	Biopsy	Stones	Follow-Up
L. L.	32	4/ 6/40	4/19/40	Heartburn; pain in right upper quadrant	Cholecysto-gastrostomy	Pancreas extremely hard	None	Cured	None	None	Perfectly well, according to report of family physician
E. C.	31	5/ 3/41	6/ 7/41	Malaise and jaundice	Choledocho-duodenos-tomy	Pancreas enlarged; hard and nodular	Severe diabetes since onset of symptoms	Cured	Chronic pancreatitis	None	Died a few weeks after his discharge from diabetic acidosis(?)
E. F.	22	12/22/42	4/ 5/44	Pain and jaundice for 3 weeks	Cholecysto-jejunostomy followed by choledocho-gastrostomy	Hard pancreas	None	Cured	Chronic pancreatitis	None	Perfectly well; gained 40 pounds (18 Kg.) in weight

it should be dissected from its bed and anastomosed to one of the hollow viscera. We have long used the "sleeve" operation as recently described by Binkley, Palmer and McCorkle.[16] For many years one of us (M.B.) has stated that anastomosis of the bile passageways to the stomach may be done with safety. Ascending cholangitis has been infrequent, and the presence of bile in the stomach has caused no distressing symptoms.

Because of the danger of infection, many surgeons have been reluctant to use the types of anastomosis referred to. We have never been deterred from performing such procedures since in our cases the incidence of infection has been low. Recently, Peterson and Cole have advocated the Roux procedure in addition to the formation of valves in the jejunum to prevent regurigitation of food.

We have found that it is not necessary to remove part or all of the pancreas in cases of chronic pancreatitis. An anastomosis of the common duct to the hollow viscera will suffice to cure the patient. It is questionable whether the magnitude of the Whipple operation or the mortality rate accompanying it justifies its use except in proved cases of carcinoma.

REVIEW OF CASES

In the accompanying table it will be noted that only 1 of the 10 patients reported on had stones in the gallbladder. This is characteristic of chronic pancreatitis. Stones in the biliary tract are exceptional in the presence of chronic pancreatitis in our experience. The age incidence is not significant. The youngest patient in the group was 22 years of age and the oldest 60. All had jaundice except 2. The earliest patient (H.H.) was subjected to choledochostomy, with T tube drainage. Five underwent cholecystoduodenostomy. In 1 case a choledochoduodenostomy was performed, and in another cholecystojejunostomy was followed by choledochogastrostomy. In all cases the pancreas was hard, and it was most difficult to differentiate between chronic pancreatitis and carcinoma. If patients operated on live over five years, this fact can be taken as reasonable evidence that cancer of the pancreas or of the papilla of Vater was not present. All but 1 of our patients lived for five years or more in good health. One patient lived for twenty-two years after the anastomosis. He died in February 1947 of coronary thrombosis.

BRIEF RFPORT OF CASES

Case 1.—H. H., aged 59, was admitted to the hospital on May 19, 1918. She had been sick for two weeks, with jaundice. There was a history of pruritus. It was impossible in this particular case to obtain a follow-up history.

16. Binkley, F. M.; Palmer, R., and McCorkle, H. J.: Experimental Implantation of the Common Bile Duct into the Intestine, Surg., Gynec. & Obst. **84**:697-703 (April 15) 1947.

Operation.—Choledochostomy, with the insertion of a T tube, was performed on May 25. The pancreas was hard, and a diagnosis of chronic pancreatitis was made. The patient was discharged on June 23, 1918.

CASE 2.—J. B., 47 years of age, was admitted to the hospital on Oct. 17, 1925. His symptoms began in August of 1925. He was seized with severe pain in the upper right abdominal region. Jaundice did not appear until several months later. He had pruritus, and the stools were acholic. The liver was enlarged about 2 inches (5 cm.) below the costal border. Cholecystoduodenostomy was performed on October 29. At operation a hard mass was found at the head of the pancreas and at the ampulla of Vater. There were no gallstones present. There was nothing unusual about the laboratory reports. The patient was discharged on Nov. 15, 1925.

Comment.—At the time of operation I classified the condition as carcinoma of the head of the pancreas. The patient lived for twenty-two years in good health and without jaundice after the operation. He died suddenly in February 1947 of coronary thrombosis.

CASE 3.—N. B., aged 34, was admitted to the hospital on Feb. 25, 1927. She gave a history of having had several attacks of pain in the right upper abdominal quadrant a year ago. Jaundice appeared a few days before her admission. Cholecystoduodenostomy was performed on February 26.

At operation the head of the pancreas was extremely hard. A few stones were removed from the gallbladder but none from the common duct. She was discharged on March 13, 1937. Her family physician has informed us that she has been perfectly well since the operation.

CASE 4.—A. H., aged 51, was admitted to the hospital on Nov. 1, 1928. Her symptoms dated back seven years, when she had pain and tenderness in the right upper abdominal region, with nausea and vomiting. Pronounced jaundice and pruritus had recently appeared. Cholecystoduodenostomy was performed on November 5. At operation the pancreas felt hard. There were no nodules present. There were no stones in the gallbladder or in the common duct. She was discharged on Dec. 4, 1928. She has been well since the operation.

CASE 5.—S. B., aged 45, was admitted to the hospital on March 7, 1933. Eight years previously she had had an attack of severe epigastric pain. This recurred mainly at night. The attacks lasted from one to four days. Jaundice or pruritus was not noticed. Cholecystoduodenostomy was performed on March 11. At operation the head and body of the pancreas were hard and nodular. A stoneless gallbladder was present. She was discharged on April 8, 1933. Her family physician reports that she is well when she is not indiscreet in her diet.

CASE 6.—K. G., aged 60, was admitted to the hospital on Feb. 6, 1938. She was well until two years before her admission when pain developed in the right upper abdominal quadrant. She lost 20 pounds (9 Kg.) in weight. Jaundice was not present. Cholecystoduodenostomy was performed on February 12. There were no stones in the gallbladder or in the common duct. However, the head of the pancreas was firm, though there did not seem to be any malignant process. She was discharged on Feb. 27, 1940.

Comment.—The patient has reported that she has never required any medication or consulted the physician for her former symptoms. She eats everything and experiences no distress.

CASE 7.—A. B., aged 49, was admitted to the hospital on March 6, 1940. For one year she had had pain in the epigastric region and in the right upper

abdominal quadrant. Jaundice was present. Cholecystogastrostomy was performed on March 9. At operation no stones were found in the gallbladder or in the common duct. The pancreas, however, was extremely hard over its entire length, and chronic pancreatitis seemed to be present. She was discharged on March 20, 1940. Her family physician reports that she has been well since the operation.

CASE 8.—L. L., aged 32, was admitted to the hospital on April 6, 1940. For six years he had had heartburn after meals, without any acute pain. Roentgenograms showed the presence of a stone in the gallbladder, but no stones were found at operation. Cholecystogastrostomy was performed on April 8. After the abdomen was opened, there was no doubt that the pancreas was the cause of the trouble. He was discharged on April 19, 1940.

His family physician reports that the patient has had no pain or discomfort since the operation.

CASE 9.—E. C., aged 31, was admitted to the hospital on May 3, 1941. For about six weeks the patient had complained of malaise and jaundice. Various studies revealed obstructive jaundice. Because of hyperglycemia, which had never been present before, the pancreas was considered the cause. Choledochoduodenostomy was performed on May 19. At operation the head of the pancreas was much enlarged, hard and nodular. There were no stones in the gallbladder or in the common duct. A biopsy was made, which showed decided fibrosing replacement of pancreatic tissue. The island tissue was relatively spared, though the islands were also involved. The patient was discharged on June 7, 1941.

Comment.—This patient died at home several weeks after operation. The physician was of the belief that the cause of death was diabetic acidosis.

CASE 10.—E. F., aged 22, was admitted to the hospital on Dec. 22, 1942. The case was an extraordinary one and will be the subject of a separate paper. In all, nine operations were performed.

For three weeks before her admission the patient complained of abdominal pain followed by jaundice. There was some nausea after meals but no vomiting. Jaundice and itching appeared a few days after the abdominal pain. At the first operation the pancreas was hard and was causing absolute obstruction of the common duct. The ninth and last operation performed was a choledochogastrostomy (Feb. 20, 1943).

Biopsy was performed on two occasions. At both times diffuse fibrosis of the pancreas was revealed.

SUMMARY

1. Chronic pancreatitis may cause complete or incomplete obstruction of the common bile duct.

2. The cause is still undetermined.

3. There may be some connection between congenital fibrocystic disease of the pancreas and chronic pancreatitis.

4. The symptoms are not always suggestive of pancreatic disease because they may simulate those of cholelithiasis or those of carcinoma of the head of the pancreas.

5. Jaundice may or may not be present in chronic pancreatitis (the majority of our patients had jaundice).

6. The diagnosis of chronic pancreatitis is difficult to establish, even after the abdomen has been opened.

7. It is necessary to differentiate between chronic pancreatitis and carcinoma of the head of the pancreas.

8. When there is doubt, a biopsy should always be made; an internal anastomosis is preferred to the use of the T tube after a choledochostomy.

9. The literature has been reviewed, and a brief review of 10 cases has been recorded.

ABSTRACT OF DISCUSSION

Dr. Allen O. Whipple, New York: I should like to emphasize one point in regard to Dr. Behrend's paper. After a thorough trial of anastomosing the gallbladder and the common duct to the stomach over a period of years, we gave it up completely because of the high incidence of cholangitis; on the other hand, in anastomosis of the common duct, especially to a vertical limb of the jejunum, there has been a remarkable reduction in that unfortunate late complication. We have been unable to get valuable information from biopsies in doubtful cases. A negative biopsy does not mean that the radical procedure should not be undertaken. In Dr. Behrend's paper a careful study of pancreatic ferments was not emphasized. That has been an extremely valuable aid in our hands in the diagnosis of both carcinoma and chronic pancreatitis and in differentiating between a growth in the head of the pancreas, one in the papilla and one in the lower end of the common duct.

Dr. Moses Behrend, Philadelphia: In answer to Dr. Whipple, I should like to say that in my paper I did refer to the danger of infection but did not have time to read it. I have been performing these various anastomoses which you were shown on the screen for nearly forty years. Infection in my cases has practically never occurred. So far as biopsies are concerned, I still believe that they are an important adjunct in the diagnosis when one is not sure.

In the case involving the woman 22 years old in whom we found chronic pancreatitis with complete obstruction the biopsy was made and the report was chronic pancreatitis. After the operation, however, I wanted to do a complete pancreaticoduodenectomy, but the internist would not allow the operation. The second biopsy also showed that the patient had chronic pancreatitis.

LEIOMYOSARCOMA OF THE STOMACH

Review of Sixteen Cases and a Report of a Case of Multiple Leiomyosarcomas of the Stomach

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A REVIEW of all the cases of leiomyosarcoma of the stomach at the Mayo Clinic has been made, first, because of the apparent increase of the frequency of this condition and, secondly, in order to review again the symptoms and pathologic findings associated with leiomyosarcomas of the stomach. We also wish to present data on a comparatively rare case of multiple leiomyosarcomas of the stomach with metastasis.

The relative infrequency of leiomyosarcoma will be seen when one compares the number of cases of surgically verified gastric carcinoma encountered at the clinic in the period 1907 through 1946, i.e., 10,000, with the number of cases of surgically verified leiomyosarcoma of the stomach, i.e., 16. This is a ratio of 625:1. However, the relative frequency of proved cases of this disease is increasing. In the ten year period from 1910 through 1919 it was found in 2 cases at the time of operation. From 1920 through 1929 only 1 case of proved leiomyosarcoma was found. In the decade from 1930 through 1939 operation was performed in 3 cases. From 1940 to July 1, 1947 the diagnosis had already been proved at the time of operation in 10 cases. The exact explanation of this phenomenon is probably found in the apparent increase of all malignant lesions. As the average age of the public increases, more persons arrive in the cancer age groups.

Ewing[1] stated that a leiomyosarcoma is a neoplasm consisting of immature smooth muscle cells of varying degrees of differentiation grouped into interlacing bundles and bands separated by a fibrous stroma, the amount of which depends on the compactness of the tumor structure. The finding of mitotic figures establishes the malignant nature of the lesion.[2]

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1. Ewing, J.: Neoplastic Disease: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928, pp. 277-279.

2. Lemon, R. G., and Broders, A. C.: A Clinical and Pathological Study of Leiomyosarcoma, Hemangioendothelioma or Angiosarcoma, and Fibrosarcoma of the Stomach, Surg., Gynec. & Obst. **74**:671-680 (March) 1942.

Leiomyosarcomas vary in structure from extremely cellular myomas of questionable malignancy to the anaplastic undifferentiated tumors of high malignancy.[3] Grossly the lesion is usually bulky, cystic or solid. It may project into the peritoneal cavity or into the lumen of the stomach. It is usually late in metastasizing.

This lesion is one of the rarest tumors of the stomach. It has been reported to comprise only 10 per cent of all gastric sarcomas. Since the ratio of sarcomas to carcinoma of the stomach is said to be only 1:100, only 1 case of leiomyosarcoma should be expected to occur for every 1,000 cases of gastric carcinoma.[4] We found the ratio existing at the Mayo Clinic to be 1:625. Various authors list lymphosarcoma as the most frequent sarcoma of the stomach, considering it to constitute between 60 and 70 per cent.[5] Fibrosarcoma is the next most frequent sarcoma, constituting about 20 to 25 per cent of all the sarcomas. Finally leiomyosarcomas constitute approximately 10 per cent of all sarcomas of the stomach.[6] Morgagni is credited with recording the first gross description of a gastric sarcoma in 1762.[7] The first report of a case of gastric sarcoma was that of Bruch in 1847. Virchow in 1863 described three myosarcomas of the stomach.[8] Other reports of leiomyosarcoma are given.[9]

CLINICAL FINDINGS

Etiology.—The exact cause of leiomyosarcomas is not known. There are, of course, many hypotheses as to the origin of this neoplasm. Embryonal rests, which Cohnheim advanced as an explanation, seem to be a probable etiologic factor.[3] This hypothesis seems eminently suited for the myomas, myosarcomas and neurogenic tumors of the stomach. It gains

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3. Pack, G. T., and McNeer, G.: Sarcoma of the Stomach: A Report of Nine Cases, Ann. Surg. **101**:1206-1224 (May) 1935.

4. Schindler, R.; Blomquist, O. A.; Thompson, H. L., and Pettler, A. M.: Leiomyosarcoma of the Stomach: Its Roentgenologic and Gastroscopic Diagnosis and Its Possible Relation to Pernicious Anemia, Surg., Gynec. & Obst. **82**:239-252 (March) 1946.

5. (*a*) Balfour, D. C., and McCann, J. C.: Sarcoma of the Stomach, Surg., Gynec. & Obst. **50**:948-952 (June) 1930. (*b*) D'Aunoy, R., and Zoeller, A.: Sarcoma of the Stomach: Report of Four Cases and Review of the Literature, Am. J. Surg. **9**:444-464 (Sept.) 1930.

6. Fenwick, W. S.: Primary Sarcoma of the Stomach, Lancet **1**:463-465 (Feb. 16) 1901.

7. Chaffin, L.: Smooth Muscle Tumors of Stomach: Review of Literature with Report of Case (Leiomyosarcoma), West. J. Surg. **46**:513-524 (Oct.) 1938.

8. Lemon and Broders.[2] Pack and McNeer.[3]

9. (*a*) Antemortem and Postmortem Records as Used in Weekly Clinicopathological Exercises, Cabot Case 25082, New England J. Med. **220**:351-353 (Feb. 23) 1939. (*b*) Christopher, F.; Benjamin, E. L., and Sauer, L. W.: Leiomyoma Malignum of the Stomach, Surgery **10**:381-386 (Sept.) 1941.

credence because these neoplasms may be multicentric. It does seem possible that sarcomas may follow a gastric ulcer, although it has not been proved. Ewing[1] cautioned against the interpretation as sarcoma of a tumor associated with an ulcer. D'Aunoy and Zoeller[5b] stated that there is little doubt that sarcomatous change could and does occur occasionally in a benign gastric ulcer. This is theoretically possible because an ulcer can stimulate prolonged formation of connective tissue, and such chronic reactions to irritations have been shown to act as etiologic factors in the production of malignant processes. Then, also, unchecked proliferation of smooth muscle during the healing phase (associated with peptic ulcer) might occur. Rieniets[10] showed that at routine necropsies benign smooth muscle tumors, or leiomyomas, were found in 16 per cent of the stomachs examined. Therefore, only a small percentage apparently undergo malignant transformation. What part trauma plays in this transformation is not exactly known.

Sex.—The majority of authors find that there is hardly any sex difference for this neoplasm. Chaffin,[7] in reviewing the literature, found that 57 per cent of 44 patients were female. Horsley and Berger[11] found no sex difference. Pack and McNeer,[3] in reviewing 9 cases of sarcoma, found that males predominated over females in a ratio of 67 to 33 per cent. In our series 8 patients were male and 8 were female. These figures vary from those found for gastric carcinoma, in which the ratio is 3:1, with males predominating.

Age.—Sarcoma as a general rule occurs in younger subjects than carcinoma. Pack and McNeer[3] found the average age in their cases to be 45 years, with a range from 24 to 65. Lemon and Broders[2] found the average age to be 50 years. In our series we found the average age to be 43.7 years. Our youngest patient was a boy 10 years old. Our oldest patient was a man 68 years of age (table 1).

Symptoms.—There are no characteristic symptoms which are pathognomonic of leiomyosarcoma. The symptoms point as often to an ulcer, with pain that responds to an ulcer regimen, as to a gastric or abdominal tumor.[12] The duration of the symptoms is longer that that of the symptoms of carcinoma. However, the three cardinal findings which would lead one to suspect this condition are (1) gastrointestinal hemorrhage, either hematemesis or melena leading to anemia, weakness and fatigue; the endogastric forms and the intramural types give rise to hemorrhage

10. Rieniets, cited by Wilbur, D. L.: Discussion on Leiomyoma of the Stomach, Proc. Staff Meet., Mayo Clin. **10**:628 (Oct. 2) 1935.

11. Horsley, G. W., and Berger, R. A.: Leiomyosarcoma of Stomach: Report of Three Cases, Ann. Surg. **112**:22-30 (July) 1940.

12. Eckhoff, N. L.: Leiomyoma of the Stomach with Report of a Case, Guy's Hosp. Rep. **91**:153-156, 1942.

when the overlying mucosa ulcerates and when the tumor becomes necrotic, which is likely to be severe and is no rare cause of death,[13] (2) epigastric distress or pain in the left upper abdominal area and (3) the discovery of a mass in the upper abdominal area either by the patient or by the physician at the time of examination. Nausea and vomiting is not a frequent symptom. It is, however, a late symptom unless the pylorus is involved. Loss of weight is only moderate. Epigastric or abdominal pain, other than that associated with ulcer-like features, is not common.

In our series the main presenting symptom was bleeding. In 69 per cent this was the presenting symptom. This bleeding was in the form of one or several attacks of hematemesis or melena. The average duration of the symptom was two years. The longest history of bleeding was given by a female patient who had had attacks of hematemesis and melena over a period of sixteen years. However, the great majority of patients had a history of bleeding for only a two or three month period. Epigastric distress or ulcer-like symptoms were present in 50 per cent of the patients. Most of these patients had been on an ulcer regimen; many had responded favorably, only to have recurrence of the epigastric distress. The average duration of these symptoms was two years and eight months. Palpable tumors were found in 7 patients, or 44 per cent. Of these 7 patients, 5 had known the presence of an abdominal mass for an average period of one year and eight months. Two of the masses were discovered by the examining physician. Loss of weight was present in only 31 per cent. The average amount of weight loss was only 13 pounds (5.9 Kg.) over a period of one year. Weakness and fatigue were present in 31 per cent of the cases. It was later found that in most of these cases bleeding had been occurring without the patient being aware of it. Vomiting was present in only 3 cases (19 per cent). This symptom is usually a late one unless the pylorus is involved. Pain in the upper part

TABLE 1.—*Age Distribution According to Decades*

Age, Yr.	Patients	Per Cent
10 to 19	2	12
20 to 29	0	0
30 to 39	3	19
40 to 49	6	38
50 to 59	3	19
60 to 69	2	12
Total	16	100

13. Holta, A.: Leiomyosarcoma Ventriculi: Three Cases, Acta radiol. **24**: 166-173, 1943.

of the abdomen not associated with epigastric distress was present in only 1 case (6 per cent).

The symptoms vary, of course, with the location of the lesion. In latent forms of growths there may be no relative gastric symptoms. Exogastric sarcomas, which are slow growing and large, may not cause any gastric symptoms. Then again the intramural or endogastric leiomyosarcomas may cause symptoms of gastric ulcer or of carcinoma.

Laboratory Data.—The great majority of the patients presented a picture of anemia. The average concentration of hemoglobin was 9.5 Gm. per hundred cubic centimeters of blood. The average erythrocyte count was 3,780,000 cells per cubic millimeter of blood. The blood smears revealed a picture of hypochromic anemia.

In 11 of the 16 cases analysis of gastric contents was performed. In 8 cases up to 58 degrees of free hydrochloric acid was present. In 3 cases no free hydrochloric acid was present. This situation varies from that in gastric carcinoma in which almost 50 per cent of the patients have low amounts of hydrochloric acid or none at all.

Roentgenologic Examinations.—In none of the 16 cases was an exact diagnosis of leiomyosarcoma of the stomach made. We realize that it is an extremely difficult task for a roentgenologist to do more than give the exact location of the neoplasm. The rest would be speculation, as this tumor does not have a distinctive roentgenologic appearance. In 8 cases (50 per cent) a diagnosis of gastric tumor, either submucous, intramural, polypoid or neoplastic, was made. In 3 cases (19 per cent) the result of the roentgenologic examination of the stomach had been interpreted as indicating no abnormality. In 2 cases (12 per cent) the diagnosis of gastric ulcer was made. In 1 case a diagnosis of carcinoma, polypoid type, was made, and in 1 case the lesion was diagnosed as an extrinsic mass. In 1 case a diagnosis of leiomyoma, intramural type, was made; the lesion in this case was a high grade leiomyosarcoma.

Kirklin and Weber[14] stated that sarcoma of the stomach is rare. Although unmistakable roentgenologic evidence of the malignant nature of the process usually can be elicited, the roentgenologist is prone, on account of its comparatively low incidence, to designate the process as carcinoma.

Schindler and his co-authors[4] wrote in regard to roentgenologic findings that the presence of a gastric filling defect, a central niche and fistulas in the lesion may be suggestive of a leiomyosarcoma. In only 1 of our cases was the presence of sinus tracts proceeding into the depth of the tumor mentioned by the pathologist when the gross specimen was exam-

14. Kirklin, B. R., and Weber, H. M., cited by Lemon and Broders.[2]

ined. However, this finding may be present more often if it is looked for carefully.

Preoperative Diagnosis.—A diagnosis of abdominal tumor was made in 10 cases (62 per cent). Splenic anemia was the diagnosis in 2 cases (13 per cent). Peptic ulcer was diagnosed in 2 cases (13 per cent). The other diagnoses were gastric carcinoma (1 case) and leiomyoma (1 case).

PATHOLOGIC FINDINGS

Grade of Lesion.—All the tumors were graded according to Broders' method of classification. In 10 cases (62 per cent) the lesions were grade 1, in 3 cases (19 per cent) grade 2 and 3 cases grade 3. There were no grade 4 lesions.

Nodal Involvement.—In only 2 cases were nodes found to be involved at the time of operation. In 1 case, in which the lesion was high grade 3, the gastric nodes were involved by direct extension. In the other case there was metastasis to a regional node. Metastasis in leiomyosarcomas may occur via the blood or lymph stream or by direct extension.[15] Metastasis is seldom early and is less extensive than it is in carcinoma. Pack and McNeer[3] gave the frequency for metastasis as 33 per cent. Our figure for leiomyosarcomas was 12 per cent. Metastasis was found in 15 per cent of Schindler and his co-authors'[14] collected series.

Location of the Neoplasm in the Stomach.—The majority of authors[16] find the lesion to be fairly well distributed throughout the stomach; this was true in our study. We found that in 4 cases (44 per cent) the lesion was located on the anterior wall, in 5 cases (31 per cent) on the posterior wall, in 3 cases (19 per cent) on the lesser curvature and in 1 case on the greater curvature. In 8 cases (50 per cent) the lesion was in the upper half of the stomach, and in 8 it was in the lower half.

Analysis of the Pathologic Specimen.—Gross Analysis: Holta[13] wrote that the lesions are found endogastrically, intramurally or exogastrically. The endogastric forms develop submucously. The mucous membrane usually remains intact for a long time until it becomes necrotic and ulcerates. These tumors are often pedunculated and are attached by a broad base. The intramural forms are usually diffuse thickenings in the muscularis. The exogastric forms are usually the largest. They frequently become soft and form cystic cavities that not rarely break into the peritoneal cavity, with peritoneal metastasis and peritonitis. All forms metasta-

15. Lyons, C. G., and Schneider, M.: Leiomyosarcoma, Am. J. Roentgenol. **49**:393-397 (March) 1943.

16. Madding, G. F., and Walters, W.: Lymphosarcoma of Stomach, Arch. Surg. **40**:120-134 (Jan.) 1940. Footnote 9*a*.

size preferably to the perigastric lymph nodes and also to the liver. Metastasis usually appears late.

In 5 cases (31 per cent) the lesion was of the endogastric and pedunculated type. This is more likely to be of a low grade of malignancy than the other types. In 9 cases (56 per cent) the lesion was of the intramural or infiltrative type, and in 2 cases (13 per cent) it was of the exogastric or expanding type. There is no explanation for these different types of growths, as there is none for the different forms of gastric carcinoma.

Ulceration of the mucosa covering the tumor is frequent in all forms. In 8 cases (50 per cent) the mucosa was ulcerative. In 3 cases (19 per cent) the leiomyosarcoma was found in a degenerating leiomyoma, with sarcomatous regions present.

In 15 cases (94 per cent) the lesion was single. In 1 case (6 per cent) there were multiple lesions (two).

TABLE 2.—*Types of Operation Performed*

Type of Operation	Cases	Per Cent
Posterior Polya	6	38
Transgastric local excision	5	31
Anterior Polya	3	19
Total gastrectomy	1	6
Billroth I (Haberer)	1	6

The average size of the lesion was 8 by 7 by 5 cm. The smallest lesion found was 4 by 3 by 3 cm. The largest lesion was 15 by 15 by 8 cm. This tumor weighed 1,194 Gm.

TREATMENT

Only one method of treatment of this condition is possible. This is surgical removal of the lesion. The tumor is not radiosensitive; therefore, radiotherapy is of no value. Chaffin[7] reported that in his collected series of 44 cases 85 per cent of the leiomyosarcomas were operable. In 26 of the cases gastric resection was performed; the mortality rate for this group was 20 per cent. In 7 cases local excision of the lesion was done. Three of the patients in this group later died from metastasis. In 5 cases palliative gastroenterostomy and in 2 biopsy alone was performed. Lahey and Colcock[17] found that of 7 patients operated on for leiomyomatous tumors of the stomach 5 (71 per cent) showed sarcomatous degeneration.

17. Lahey, F. H., and Colcock, B. P.: Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of Stomach, Ann. Surg. **112**:671-686 (Oct.) 1940.

In the light of their experience they expressed the belief that leiomyosarcoma of the stomach should be treated by high subtotal gastrectomy rather than by local removal alone.

In our series of cases (table 2) subtotal gastrectomy was performed in 10 (63 per cent). Total gastrectomy was performed once. Transgastric local excision was performed five times (31 per cent).

Of the 16 patients we were able to trace 15. Two of the 16 died while in the hospital. Six patients are still alive. It has been only three months since the time of operation on 1 patient. Two of the patients have now lived more than five years, and 3 have lived from one to four years since their operation. Seven of the 15 patients have died. Three died within the first year, 1 died between the first and second years, 2 died between the second and third years and 1 died between the third and fourth years. One of the 7 patients died from a colloid carcinoma of the cecum two years and six months after operation.

Five of the 16 patients had transgastric local excision of the lesion. At last report 2 patients were still living after more than four years. One patient died while in the hospital. Her death was attributed to cardiac causes. The remaining 2 patients have died since leaving the hospital. One of them lived one year and eight months. His death was due to generalized sarcomatosis. The other patient lived three years and four months, after which a recurrent sarcoma occurred.[18] The lesions in these 2 cases occurred near the cardia of the stomach. Remarks were made that total gastrectomy would have to be done, but the tumor mass did not seem to invade the stomach wall. Hence it was decided to do a local excision of the lesion.

Prognosis.—The prognosis for these patients is better than that for those who have carcinoma of the stomach. Pack and McNeer[3] stated that the life expectancy for untreated patients is eighteen months. Our series shows that 8 of the patients with leiomyosarcoma of the stomach have lived twenty months or longer after their operation. The longest survivor has lived more than seven years since his operation.

REPORT OF A CASE

On July 16, 1947, a white woman aged 46 years reported to the Mayo Clinic. She complained of intermittent epigastric distress, which she had felt for ten years. This distress was relieved by food and alkalis. There was also an accompanying distress at night. Sixteen years previously she had had an attack of hematemesis and tarry stools. In 1941 she had had another attack of bleeding. Roentgenograms of the stomach had been normal. Antacids and a bland diet were prescribed, with relief of the symptoms. In February 1947 the patient had had another attack of melena, which lasted three days. At this time erythrocytes had numbered 2,000,000 per cubic millimeter of blood. She had had five transfusions and had been hos-

18. Mayo, C. W.: Leiomyosarcoma of Stomach Two Years After Operation: Report of Case, Proc. Staff Meet., Mayo Clin. **12**:587 (Sept. 15) 1937.

pitalized for three weeks. In June 1947 she had had another bout of bleeding, and rehospitalization had been necessary.

Physical examination revealed no abnormalities. Laboratory studies revealed a concentration of hemoglobin of 10.4 Gm. per hundred cubic centimeters of blood. Erythrocytes numbered 4,430,000 in each cubic millimeter of blood. Analysis of gastric contents revealed 46 degrees of free hydrochloric acid and 60 degrees of total hydrochloric acid. The stools contained occult blood. Roentgenograms of the stomach revealed a large polypoid tumor in the lesser curvature. The lesion was in the distal half of the stomach, and the roentgenologist thought that it might be intramural, with mucosal involvement.

On July 28, 1947, one of us (W.W.) performed subtotal gastrectomy. On the lesser curvature of the stomach 4 cm. above the pylorus an encapsulated leiomyosarcoma, grade 2, was found. The tumor was submucosal and semipedunculated. Two dimples were present on the overlying mucosa, probably representing healed ulcers. Just proximal to this tumor there was a second subserosal leiomyosarcoma, grade 2, 2 cm. in diameter. One regional metastatic node was found. Chronic duodenitis was present. Cholecystectomy was also performed because of hydrops of the gallbladder. One large cholesterol stone was present. The patient had an uneventful postoperative course. She left the hospital eleven days after operation.

This case is indeed a rarity as it is the only one of multiple leiomyosarcoma which was found in our files. Jordan[19] reported 1 case in 1938.

SUMMARY

Sixteen cases of leiomyosarcoma of the stomach have been reviewed. It was found that the average age of the patients was 43.7 years, the youngest being a boy 10 years of age. Half of the patients were male. The three cardinal symptoms were gastrointestinal hemorrhage (69 per cent), epigastric distress and ulcer-like symptoms (50 per cent) and palpable tumor (44 per cent).

Anemia was encountered in almost all cases. In 73 per cent of the cases free hydrochloric acid was present in the stomach. It is difficult to make a positive diagnosis of leiomyosarcoma on roentgenologic examination, although the presence of an abdominal tumor is easily determined. The majority of the lesions were low grade, 81 per cent being grade 1 or 2. Nineteen per cent were grade 3. In only 12 per cent of the cases was there metastasis. Fifty per cent of the lesions were in the upper half of the stomach and 50 per cent in the lower half. Eight of the 15 patients traced have survived for periods of from twenty months to seven years.

In 5 cases transgastric excision of the lesion was performed. Only 2 of the 5 patients are still living (both four years). One patient died in the hospital. Two patients died from recurrent sarcomatosis. It is felt that only subtotal gastrectomy should be done for these lesions and total gastrectomy in cases in which it seems feasible.

Finally, data on a case of multiple leiomyosarcomas of the stomach with metastasis have been presented.

19. Jordan, S. M.: A Case of Multiple Leiomyosarcomata of the Stomach, S. Clin. North America **18**:683-686 (June) 1938.

SURGICAL PROBLEM OF PERIAMPULLARY CANCER

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IN NO GROUP of intra-abdominal tumors has the presence of cancer been so consistently and early indicated by distressing and compelling symptoms as in those lesions producing obstructive jaundice. The scope of operations for gastric, colonic and rectal cancer has increased greatly to include not only the organ involved and its immediate lymphatic tributaries but also adjacent invaded structures regardless of the demand made on already altered physiologic economy. However, cancer producing biliary obstruction discouraged for many years the application of the acceptable surgical principles involved in excision of a tumor and in dissection of its lymphatic bed in continuity. It remained for Whipple and his colleagues,[1] encouraged by their studies on resection of the body and tail of the pancreas in patients with hyperinsulinism and discouraged by the not unusual complications of local excision of periampullary tumors, to redefine the issue and to plan, execute and popularize an operative attack based on the surgical principles acceptable for the treatment of cancer elsewhere in the body. As a result of their historic article, many papers dealing with limited experiences in radical pancreaticoduodenal resection have been published since 1935, superseding the previous discussions of palliative operations for neoplastic biliary obstruction.

The universal acceptance of Whipple's radical operation and his subsequent modifications and extensions and of those of Brunschwig, Trimble, Orr, Pearse and Hunt was a manifestation of the need for a defintive stand on this fundamental surgical problem rather than a continuation of palliative operations already known to be associated with a high operative mortality and with end-results of questionable value. The problems encountered in the surgical treatment of obstruction of the common duct due to choledocholithiasis alone, especially the problem of altered clotting mechanism in obstructive jaundice, predicted that a most discouraging

From the Gastric Service of the Memorial Hospital for Cancer and Allied Diseases.

1. Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, Ann. Surg. **102**:763-779, 1935.

evolutionary period would ensue. Although four decades separate the prophetic operation of Codivillo[2] and the innovation of Whipple, the procedure of pancreaticoduodenectomy has become of age. A changed viewpoint even in the last few years is apparent by a comparison of Whipple's[3] declaration in 1942 that the operation was unquestionably in the experimental stage with the recent utterance of Pearse,[4] who posed the question: "Should we standardize the reconstruction after pancreaticoduodenectomy?"

Because of the limited number of cases of periampullary cancer occurring in each operator's practice and the necessity for a large number of adequate, detailed reports in assembling collective and cumulative data for surgical analysis, we wish to present our experiences in 5 cases of peripapillary cancer.

SCOPE OF THE PROBLEM

The problem of neoplastic biliary obstruction has necessitated surgical attack on three organs, i.e, the biliary duct system, the pancreas and its duct system and the duodenum. Aside from the prognosis, the surgical problem is the same, though the histogenetic and the pathogenic background are different and may be the cause of a varied clinical syndrome dependent on the relationishp of the lesion to the biliary duct system itself.

Outerbridge[5] in 1913 first commented on a fact of remarkable clinical importance in his review of 110 cases of periampullary cancer reported up to that time. The occurrence of metastasis was noted only twenty-five times (22 per cent), and in a few additional instances limited direct extension of the cancer into connective tissue lying between the duodenum and the pancreas itself was found. He stated that in three fourths of his collected cases the growth was limited to the papilla of Vater and its immediate surroundings and death occurred apparently as a result of interference with the flow of bile and not as a result of other complications of the cancer.

One of us[6] in 1937 reviewed the problem of carcinoma of the duodenum and indicated the importance of the periampullary region by giving

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2. Codivillo, cited by Gray and Sharpe.[10]

3. Whipple, A. O., in discussion on Harvey, S. C., and Oughterson, A. W.: The Surgery of Carcinoma of the Pancreas and Ampullary Region: Report of Six Additional Cases, Ann. Surg. **115**:1066-1090, 1942.

4. Pearse, H. E.: Should We Standardize the Reconstruction After Pancreaticoduodenectomy? Surgery **20**:663-669, 1946.

5. Outerbridge, G. W.: Carcinoma of the Papilla of Vater, Ann. Surg. **57**:402-426, 1913.

6. Hoffman, W. J., and Pack, G. T.: Cancer of the Duodenum: A Clinical and Roentgenographic Study of Eighteen Cases, Arch. Surg. **35**:11-62 (July) 1937.

the frequency of cancer in the various portions as follows: supra-ampullary, 24.9 per cent; periampullary, 61.9 per cent, and infra-ampullary, 13.1 per cent. In 1939 Lieber, Stewart and Lund[7] abstratced reports of 399 cases of periampullary carcinoma of the duodenum in the literature, 222 of which were considered acceptable for analysis. More recently, Berger and Koppelman[8] brought the collected cases of primary carcinoma of the duodenum up to 670; 386 of these were considered to be proved cases, and in 65 per cent of the entire group the cancer was periampullary in origin. While from a pathologic standpoint, Lieber, Stewart and Lund classified the lesions under six different groups according to their site or origin, it was found that in practically all cases they resolved themselves into carcinoma involving all the epithelial structures of the papilla of Vater, including the intestinal mucous membrane covering it, or cancer involving all these structures without involvement of the duodenal mucosa. Though small and still confined lesions of the different structures were found arising from either the epithelium in the ampulla, the duct of Wirsung or the terminal portion of the common duct, the majority of the cancers were so invasive that even the pathologist studying the resected specimen could not ascertain the exact point of origin. This would indicate that a classification on the basis of extent of involvement at the time of examination is the most useful one and, therefore, that periampullary cancer as the surgeon sees the condition, is a fairly definite pathlogic entity.

Of important consideration in the analysis of these tumors is the fact that in 182 of the 222 cases all the epithelial structures of the papilla of Vater were involved including the intestinal mucous membrane. In this group metastasis or extension of the cancer occurred in 43 per cent, while in the group of 33 cases in which all the epithelial structures exclusive of the duodenal mucous membrane were involved extension or metastasis occurred in only 27 per cent. It would seem that the spread or invasiveness has clinical importance, possibly on the basis of the time factor, and indicates the need for early surgical intervention in cases of jaundice. In Hoffman and Pack's series of 18 patients metastasis had occurred in 33 per cent. Orr[9] noted extension beyond the confines of the ampulla in 11 of the 18 patients in his series, or in 62 per cent of the patients with various types of cancer necessitating pancreaticoduodenal resection. Gray and Sharpe[10] noted metastasis late when it occurred at all,

7. Lieber, M. M.; Stewart, H. L., and Lund, H.: Carcinoma of the Peripapillary Portion of the Duodenum, Ann. Surg. **109**:219-245 and 383-429, 1939.

8. Berger, L., and Koppelman, H.: Primary Carcinoma of the Duodenum, Ann. Surg. **116**:738-750, 1942.

9. Orr, T. G.: Pancreaticoduodenectomy for Carcinoma of the Ampulla and Ampullary Region, Surgery **18**:144-158, 1945.

10. Gray, H. K., and Sharpe, W.: Surgical Treatment of the Papilla of Vater, Surgery **14**:831-846, 1943.

and Baggenstoss[11] reported that in 15 of 28 cases the cancer of the papilla had not metastasized even though death had occurred. These figures in general corroborate Outerbridge's conclusion that in the great majority of cases periampullary cancer causes death by the effects of biliary obstruction alone and that technically resection should be possible, with the possibility of cure.

It is recognized that the greatest hope of cure is found in connection with periampullary cancers. Dixon,[12] however, after studying 45 patients with operable tumors and 4 patients with nonsurigcal malignant tumors in the duodenum, exclusive of those arising in the papilla, stated that the bad prognosis formerly given was based on previous impressions gained from studies at necropsy and that in his cases of duodenal cancer amenable to surgical treatment metastasis to regional lypmh nodes did occur relatively early but that there was a long latent period before the cancer spread to distant sites. This would seem to justify radical dissection of tumors in this region, and yet in 4 of the 45 cases in the series the cancer was segmentally resected and in 1 it was locally excised. Four cancers were removed by radical pancreaticoduodenal excision.

The operability rate of 9.0 per cent for suprapapillary cancer and 18.9 per cent for infrapapillary cancer in the cases collected by Berger and Koppelman indicates that cancers in these sites do not cause early symptoms as do the periampullary tumors. Their failure to list a single five year survival in this group suggests the necessity for a more radical surgical procedure in order to improve the end results. The substitution of total duodenectomy and resection of the head of the pancreas for subtotal procedures should increase the resectability rate and improve the number of five year definitive cures.

Judd and Hoerner[13] analyzed the data on 179 patients subjected to surgical intervention for cancers originating either in the head of the pancreas or in the ampulla of Vater and found the primary site to be in the pancreas in 158 cases and in the ampulla in 21 cases, a ratio of 7.5 to 1. Only three of Cattell's[14] radical resections were for cancer of the pancreas, and thirteen were for ampullary cancers, a fact which caused him to conclude that pancreaticoduodenal resection at present offers little

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11. Baggenstoss, A. H.: Major Duodenal Papilla: Variations of Pathologic Interest and Lesions of the Mucosa, Arch. Path. **26**:853-868 (Oct.) 1938.

12. Dixon, C. F.; Lichtman, A. L.; Weber, H. M., and McDonald, J. R.: Malignant Lesions of the Duodenum, Surg., Gynec. & Obst. **83**:83-93, 1946.

13. Judd, E. S., and Hoerner, M. T.: Surgical Treatment of Carcinoma of the Head of the Pancreas and the Ampulla of Vater, Arch. Surg. **31**:937-942 (Dec.) 1935.

14. Cattell, R. B.: Pancreatoduodenal Resection: A Preliminary Report of Eighteen Cases, New England J. Med. **232**:521-526, 1945.

hope in extensive carcinoma of the head of the pancreas. Brunschwig[15] performed eight radical resections for carcinoma of the body of the pancreas, with a 50 per cent operative mortality. One patient survived three years and eleven months, 1 five weeks, 1 five and one-half weeks and 1 is still living. This corroborates Cattell's findings. Whipple[16] admitted that cancers of the head of the pancreas and of the duodenum proper are less favorable than ampullary cancers, but he added that patients with early cancers may be benefited by the operation. Saltzstein and Rao[17] have recently shown that cancer of the head of the pancreas is not always discouraging, as evidenced in an autopsy report on a patient who underwent a palliative cholecystogastrostomy for an adenocarcinoma of the pancreas of ductal type and of grade II histologic malignancy. The process was still an entirely local one four years after operation and had shelled away from the bed of the pancreas. In Cole and Reynolds'[18] series of 5 cases the tumor occurred in the head of the pancreas in 4. In 8 patients in Dennis and Varco's[19] series the cancer was situated in the head of the pancreas; in 3 it was located in the common bile duct and in 3 in the ampulla of Vater. Of thirty radical resections reviewed by Waugh and Clagett[20] at the Mayo Clinic up to Jan. 1, 1946, seventeen were for cancers in the head of the pancreas, ten were for cancers in the ampulla and three others were necessitated by infiltrating cancers in the stomach or duodenum. These authors concurred with Cattell and Whipple in the belief that the operation is most discouraging when performed for pancreatic cancer, but the use of pancreaticoduodenal resection to increase the survival rate in cancer of the stomach gives hope, as do the reports of Brunschwig,[21] Cole and Reynolds and Child[22] on extending the scope of

15. Brunschwig, A.: The Surgical Treatment of the Body of the Pancreas, Ann. Surg. **120**:406-416, 1944.

16. Whipple, A. O.: Surgical Treatment of Tumors of the Pancreas, in Pack, G. T., and Livingston, E. M.: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940. vol. 2, chap. 74, pp. 1333-1340.

17. Saltzstein, H. C., and Rao, J.: Carcinoma of the Pancreas Still Local at Autopsy Four Years After Palliative Operation, Arch. Surg. **53**:435-440 (Oct.) 1946.

18. Cole, W. H., and Reynolds, J. T.: Resection of the Duodenum and Head of the Pancreas for Primary Carcinoma of the Head of the Pancreas and Ampulla of Vater, Surgery **18**:133-143, 1945.

19. Dennis, C., and Varco, R.: Neoplastic Biliary Obstruction: An Improved Type of Radical Pancreaticoduodenectomy for Ampullary and Pancreatic Cancers, Surgery **20**:72-81, 1946.

20. Waugh, J. M., and Clagett, O.: Resection of the Duodenum and Head of the Pancreas for Carcinoma, Surgery **20**:224-232, 1946.

21. Brunschwig, A.: Total Pancreatectomy, Total Gastrectomy, Total Duodenectomy, Splenectomy, Left Adrenalectomy and Omentectomy in a Diabetic Patient; Recovery, Surg., Gynec. & Obst. **80**:252-256, 1945.

(Footnotes continued on next page)

the operation. These more recent applications of the procedure are interesting in the light of Billroth's[23] heroic attempt to perform it as long ago as 1884 and of Mikulicz' observation on the "enormous" increase in mortality entailed in operations for removal of the stomach when the pancreas itself was included in any way.

The variable experiences of individual surgeons are represented in Whipple's résumé of radical pancreaticoduodenal resections up to April 1, 1942. Twenty-seven of a total of sixty-four cancers were located in the pancreas, twenty-one were situated in the ampulla of Vater, nine were carcinomas of the duodenum proper, one was a duodenal sarcoma, five were carcinomas of the common bile duct and in 1 instance the operation was done for chronic pancreatitis. The scope of radical pancreaticoduodenal resection, therefore, includes a wide variety of pathologic lesions whose resection is a common surgical problem. The variability of the lesions and the attendant prognosis will demand a much greater collection of cases than the last ten years of surgical experience has afforded in order to yield a true indication of what can be expected from successful resection.

THE DEVELOPMENT OF RADICAL PANCREATICODUODENAL RESECTION

The continued use of local excision in the management of tumors in or along the biliary tract from Halsted's[24] first successful transduodenal excision in 1898 to the time of Hunt and Budd's[25] collective review in 1935 represented what was generally accepted as a radical procedure, though the last two authors stated that by "rather conservative methods of radical extirpation" they referred to the "direct re-implantation of the common duct and pancreatic ducts into the duodenum, instead of extensive anastomoses between gall bladder and stomach, duodenum or jejunum, to provide internal drainage of the biliary tract." The operative mortality in the 76 cases studied was 38.1 per cent. By 1942 Hunt[26] was

22. Child C. G., III: Pancreaticojejunostomy and Other Problems Associated with the Surgical Management of Carcinoma Involving the Head of the Pancreas: Report of Five Additional Cases of Radical Pancreaticoduodenectomy, Ann. Surg. **119**:845-855, 1944.

23. Billroth, T., cited by Pfeiffer, D. B., in discussion on Whipple, Parsons and Mullins,[1] pp. 776-777.

24. Halsted, W. S.: Contributions to the Surgery of the Bile Passages, Especially of the Common Bile Duct, Bull. Johns Hopkins Hosp. **11**:1-11, 1900.

25. Hunt, V. C., and Budd, J. W.: Transduodenal Resection of the Ampulla of Vater for Carcinoma of the Distal End of the Common Duct, Surg., Gynec. & Obst. **61**:651-661, 1935.

26. Hunt, V. G.: Surgical Management of Carcinoma of the Ampulla of Vater and the Periampullary Portion of the Duodenum, Ann. Surg. **114**:570-602, 1941.

able to bring the total cases to 124, though this included 15 in which radical resection of the head of the pancreas and the duodenum was performed. It was significant that the mortality rate for transduodenal excision (29 per cent) exceeded that for the truly radical procedure (26.6 per cent). Despite the high operative mortality and although 30 per cent of the survivors died within the first year, 41 per cent of the patients were living and well, the longest period of survival being nine years. These figures contrast most favorably with those for purely palliative procedures used for carcinomas of the head of the pancreas. For example, Sallick and Garlock[27] stated that the immediate mortality rate averages between 30 and 50 per cent. They quoted various authors' mortality figures, i.e., Fraser's 51.8 per cent in a large compiled series of cholecystogastrostomies, Oppenheimer, Glass and Netter's 44.1 per cent for primary internal drainage, Eliason and Johnson's 40 per cent for cholecystoenterostomy, Cohen and Colp's 32 per cent, Zollinger and Kevorkian's 31 per cent and Coller and Winfield's 26 per cent. Sallick and Garlock were able to reduce the operative mortality to 11 per cent by doing external biliary drainage only. The over-all mortality in 106 cases was 33 per cent in the decade from 1930 to 1939. These figures concern the palliative surgical treatment of pancreatic neoplasm alone, which admittedly may give a slightly more discouraging picture than is obtained in the treatment of periampullary or combined periampullary and pancreatic lesions in so far as the lesion would be of longer duration and more deterioration of the patient would be expected. Yet it is indicated that either palliative procedures or restricted excisional operations were attended with high mortality rates, though the latter did offer considerable hope.

In reviewing the causes of death, Hunt stated that although hemorrhage could be named as the direct cause in 31.5 per cent of the cases occurring in the period from 1898 to 1941 "it is more probable that the cause of death was hemorrhage in 50 per cent of the cases had the cause of death been stated." The cause of death was not stated in 36.8 per cent of the cases. The end of this period coincides with the development of vitamin K, an advantage denied the era of local excision, so that more radical operations were in order on the basis of a successful means of controlling 50 per cent of the anticipated mortality, not to mention the advantages of massive transfusions to forestall shock, both early and late, the more liberal use of chemotherapeutic drugs and, more recently, the use of antibiotics to control the complications of infection.

The development of the radical procedure of pancreaticoduodenal resection since the original two stage operation of Whipple, Parsons and

27. Sallick, M. A., and Garlock, J. H.: Obstructive Jaundice Due to Carcinoma of the Pancreas, Ann. Surg. **115**:25-31, 1942.

Mullins has entailed changing procedures to meet the shortcomings of the first operation which soon became manifest. Cholecystogastrostomy was superseded by cholecystojejunostomy, either a loop or a closed segment of jejunum being used, in order to sidetrack the gastrointestinal stream from the biliary-gastrointestinal anastomosis to prevent ascending cholangitis. The replacement of the gallbladder with the common duct in the anastomosis was occasioned by both the tendency of the gallbladder to contract and to obstruct free biliary drainage and the frequency of "blow-out" of the ligated end of the common duct. The principle of choledochojejunostomy is now generally accepted, as is the principle of performing it proximal to the gastrojejunal anastomosis except in procedures in which the food current is by-passed by means of a lateral enteroenterostomy. More recently, pancreaticojejunostomy has become a more or less standard part of the operation, not altogether because of the problem of alimentation but to obviate the tendency toward the formation of a pancreatic fistula. The recent history of pancreaticoduodenal resection has been given in detail by Orr, Whipple[28] and Pearse; the last author states that no fewer than twenty-nine different ways of doing this operation have been described.

SYMPTOMATOLOGY AND DIAGNOSIS

All our patients had symptoms which were gradual in onset. The predominant initial complaints of 4 of the patients were painless jaundice and itching. The patient in case 4 alone presented epigastric pain as a symptom, which was followed by intermittent jaundice. The presenting symptom of painless jaundice contrasts with that in Orr's[29] series of 82 cases of ampullary and pancreatic cancer, in which pain was an outstanding symptom in 75 per cent of the cases. Pain was also a symptom in 50 per cent of a series reviewed by Ottenberg and Colp.[30] Twenty-four of Sharpe and Comfort's[31] 40 patients had experienced some kind of pain; in 16 of the 24 it was the chief complaint. All our patients had insidious anorexia, with loss of weight. An enlarged liver, with a distended gallbladder, was found on physical examination of 2 patients, and all patients presented a distended gallbladder and common duct at the time of initial operation, entirely supporting the observations of Cour-

28. Whipple, A. O.: Observations on Radical Surgery for Lesions of the Pancreas, Surg., Gynec. & Obst. **82**:623-631, 1946.

29. Orr, T.: Surgical Treatment of Carcinoma of the Pancreas and Ampulla of Vater, Texas State J. Med. **42**:183-188, 1946.

30. Ottenberg, R., and Colp, R.: Diagnosis of Surgical Jaundice, New York State J. Med. **37**:1011-1017, 1937.

31. Sharpe, W. S., and Comfort, M. W.: Carcinoma of the Papilla of Vater: Clinical Features in Forty Cases, Ann. J. M. Sc. **202**:238-245, 1941.

voisier.[32] This indicates the value of the observation as far as the surgeon is concerned.

The occurrence of chills and fever in 1 patient was not unusual. Sharpe and Comfort noted that they have been observed in from 12 to 33 per cent of the reported cases of periampullary lesions.

The symptom of melena in cases 3 and 4 and a high degree of secondary anemia in cases 2, 3 and 4 were significant as they were a manifestation of ulcerating duodenal lesions, which when present in obstructive jaundice should point strongly to an ulcerated peripapillary tumor. Allen[33] noted that the presence of occult blood in the stool not otherwise accounted for should make one suspect a duodenal tumor. He considered it to be probably the most valuable aid in the differentiation of benign diseases and malignant tumors of the duodenum. One patient had troublesome diarrhea, which subsided without any treatment.

The first point in the diagnosis of neoplastic biliary obstruction is awareness of the condition. Sharpe and Comfort analyzed 40 cases of periampullary lesions in 1941 and found that the possibility of carcinoma of the ampulla was considered in only 1 case though in 38 the diagnosis indicated that obstruction of the common bile duct was present. When there is obstructive jaundice the diagnostic survey is comparatively easy. Jaundice was present in all but 4 of the 222 cases collected by Lieber, Stewart and Lund, occurring at the onset of the condition in 136 cases and later in 82. In the latter group it occurred at an interval of three to five months after the onset of symptoms such as malaise, chills and fever, dyspepsia, vomiting, diarrhea and constipation. It would appear that the strategic position of the peripapillary lesion usually produces the troublesome symptom of jaundice, which demands early medical consultation.

In carcinoma of the pancreas the diagnosis is not easily established. While painless jaundice was present in our patient with pancreatic cancer and proved to indicate an early lesion, this is not the usual early initial symptom. Kaplan and Angrist,[34] studying the mechanism of jaundice in cancer of the pancreas, noted that in the absence of jaundice the diagnosis was almost invariably missed and it was only when the biliary tract was affected secondarily that recognizable symptoms were noted. Only 19 of their 39 patients presented jaundice at autopsy, while the clinical records showed that a variable syndrome of loss of weight, anorexia and weakness was the most constant finding. Pain was present in 23 cases, a more

32. Courvoisier, L. G., cited by Colcock, B. P.: Courvoisier's Law, Lahey Clin. Bull. **4**:222-223, 1946.

33. Allen, C. I.: Primary Carcinoma of the Deuodenum with a Report of Eleven Cases, Am. J. Surg. **40**:89-101, 1938.

34. Kaplan, N., and Angrist, A.: The Mechanism of Jaundice in Cancer of the Panceas, Surg., Gynec. & Obst. **77**:199-204, 1943

common symptom than jaundice. In this type of disease the operation has offered less because of the difficulty in palpating and investigating the deep-seated site and probably because it is thought of in terms of biliary obstruction alone so that only when a mass is palpable or when the growth has encroached on biliary drainage is cancer considered, which in most cases is late. Ransom[35] has noted that pain was a prominent symptom in two thirds of his series of patients with carcinoma of the pancreas and the extrahepatic bile ducts, contrary to the usual statement that the clinical picture of carcinoma of the pancreas is one of progressive painless jaundice. He noted that the clinical picture often simulated that present in cases of stones in the common duct. Regardless of the location of the neoplasm, loss of weight was the symptom which was present in the largest number of cases. Only by a consideration of the possibility of latent pancreatic cancer in the presence of a vague syndrome of pain in the upper abdominal area, loss of weight and anorexia will early exploration result in an increase in the number of resectable lesions.

Roentgenologic studies of our patients have been of help on 2 occasions, though in case 4 the fusiform constriction in the region of the second portion of the duodenum was thought to be due to an aberrant annular pancreas.

Laboratory studies have not been of great value in this series of cases because of the variable stages at which the patients presented themselves.

We do not wish to discuss the entire problem of diagnosis in obstructive jaundice at this time, but we should like to call attention to Gray and Sharpe's observation which indicates that each month's delay in the proper treatment of neoplastic biliary obstruction is of great significance. In a series of cases in which palliative operations alone were in order from one week to thirty months, with an average of six and a half months, had elapsed between the onset of symptoms of obstruction of the common duct and any attempt at surgical treatment, while in the group in which some type of removal was possible the duration of symptoms averaged only five and a half months. Lieber, Stewart and Lund have shown this more clearly by comparing the preoperative illness in patients who died with that in patients reported living and well at the end of the period of their study. The former group were ill for an average of about seven months, and the latter were ill for an average of only two months. The patients who lived for less than one month postoperatively were ill for an average of about six months before operation. It is therefore indicated that the duration of jaundice may be an index both to resectability and to prognosis. When a diagnosis of obstructive jaundice is made, early sur-

35. Ransom, H. K.: Carcinoma of the Pancreas and Extra-Hepatic Bile Ducts, Am. J. Surg. **40**:264-281, 1838.

gical intervention is indicated if a good respectability rate is to be attained and if long survival is to follow the operation for peripapillary cancer.

Difficult as an early clinical diagnosis may be, the identification of cancer at the operating table may be as obscure. In cases 3 and 4 former biopsies showed chronic pancreatitis only. In another case in our series in which radical resection was performed, not reported in this communication because the lesion did not prove to be carcinoma, the gross appearance at the first stage of the operation, done elsewhere, was typical of cancer, and at the time of the second procedure, six weeks later, the resection was performed because of a hard mass confined to the head of the pancreas which when probed was found to obstruct completely the common duct. While the condition was thought to be cancer of the head of the pancreas, the pathologist found the lesion to be chronic pancreatitis. Six operations have been performed for lesions which grossly appeared to be cancer, with one error in diagnosis, which, if resectable lesions only are considered, is an error of 16.6 per cent. The problem of diagnosis at the operating table is difficult and uncertain, and it is still being sought, as Halstead stated, to "make the diagnosis in other ways." The use of Lyon's duodenal drainage to obtain an aspirate for Papanicolaou studies may be of great promise, as shown in 1 of our recent cases.

COMPLICATIONS OF THE OPERATION FOR PERIAMPULLARY CANCER

All except one complication have been obviated by the evolution of the operation of radical resection as applied to cases of periampullary cancer. Ascending cholangitis has been prevented by placing the biliary-gastrointestinal anastomosis proximal to the site of the gastroenterostomy, but the need for a longer loop is still apparent in the procedure described in case 4. While the pancreatic ducts were ligated when they could be identified and the stump was carefully closed with fine silk in each case, pancreatic fistula has been a problem in three radical resections as well as in an unreported radical pancreaticoduodenectomy for chronic pancreatitis. This experience indicates the wisdom of performing pancreaticojejunostomy if only to avoid the troublesome drainage. Orr stated that he had not encountered a fistula in any case in which pancreaticojejunostomy was performed. The use of a small catheter inserted into the pancreatic duct and subsequently implanted into the jejunum, as described by Whipple, Pearse and Varco, seems to be the soundest surgical principle in providing for mucosa to mucosa apposition in this anastomosis. On 2 occasions ducts could not be identified when the radical resection was performed and the procedure popularized by Child in which either an end to end or an end to side anastomosis of the stump of the pancreas to

the lumen of the jejunum is used would have been in order. Despite permanent occlusion of the pancreatic ducts in 2 patients, no obvious deficiency of pancreatic enzymes was observed.

The manner in which the patients presented themselves did not offer an opportunity for single stage, radical pancreaticoduodenectomy.

REPORT OF CASES

CASE 1.—J. DeS., a 66 year old man, was referred from the Head and Neck Department of the Memorial Hospital on March 16, 1937. He had been a patient in that clinic since Jan. 23, 1935, for a recurrent papillary epidermoid carcinoma of the buccal mucosa. Radiation therapy was effectual, and in regular check-up examinations he was always free from recurrence of the disease. On one of his routine visits, on March 16, 1937, jaundice was noted. It had appeared nine days before, and two days after it was followed by intense itching and loss of appetite. There was no pain. During this time he lost 8 or 9 pounds (3.6 to 4 Kg.) because of the anorexia. There was no vomiting, hematemesis or melena. There was no previous history of gallbladder colic or qualitative dyspepsia.

Physical examination revealed a middle-aged man who had apparently lost considerable weight. He said his previous weight was 172 pounds (78 Kg.), but with only a hospital gown on it was 138 pounds (62.6 Kg.). The margin of the liver was palpable 6 cm. below the costal margin, and it was smooth and nontender. The gallbladder was palpable. No other masses were felt.

Laboratory studies showed a hemoglobin content of 75 per cent, a red blood cell count of 4,224,000 and a white blood cell count of 5,600 with a normal differential distribution. The icteric index was 33, blood urea nitrogen 15.8 mg. per hundred cubic centimeters and the blood sugar 83 mg. per hundred cubic centimeters. Urinalysis revealed a specific gravity of 1.020, an acid reaction, a trace of albumin and no sugar; bile was present. A roentgenogram of the abdomen revealed no evidence of calculus in the region of the gallbladder or its ducts, and the gallbladder could not be visualized after oral administration of "keraphen" (preparation of iodothaleine sodium). Gastrointestinal roentgenograms revealed approximately 30 per cent retention at six hours, but no evidence of carcinoma of the stomach was seen. The roentgenologic diagnosis was duodenal ulcer, with pyloric obstruction.

A presumptive clinical diagnosis of carcinoma of the head of the pancreas or of the ampulla of Vater was made. Choledocholithiasis was not considerad as a likely diagnosis.

On April 12, 1937, an exploratory laparotomy, performed through a right paramedian incision with the patient under spinal anesthesia produced by tetracaine hydrochloride, revealed a small amount of greenish fluid in the abdominal cavity, green discoloration of the liver and pronounced jaundice of all the abdominal organs and the mesenteric fat. The gallbladder was enlarged, measuring 10 by 8 cm. No stones could be palpated. There seemed to be a small tumor in the region of the ampulla of Vater, but the exact site of the origin of this tumor could not be determined. A cholecystogastrostomy was done, a large stoma of approximately 4 cm. in diameter being made (fig. 1*A*).

By April 26, the fourteenth postoperative day, the icteric index had dropped to 22. Then the second phase of the operation was done, again with spinal anesthesia induced by tetracaine hydrochloride. Laparotomy through a left upper rectus incision revealed that the cholecystogastrostomy wound was well healed. A

gastroenterostomy was performed posteriorly in the usual manner (fig. 1*B*). By the nineteenth postoperative day the icteric index was 16.

On May 24 the twenty-eighth day after the second operation, laparotomy was again performed, the first right rectus scar being excised. A mass could be palpated in the head of the pancreas and appeared to be limited to that region. One small node was encountered during the dissection. The cystic and common bile ducts were both distended, and their exact point of anastomosis could not be visualized. The duodenum was mobilized from its lateral aspect. The bile ducts were isolated, and the common duct was excised about 2 cm. proximal to its point of entrance to

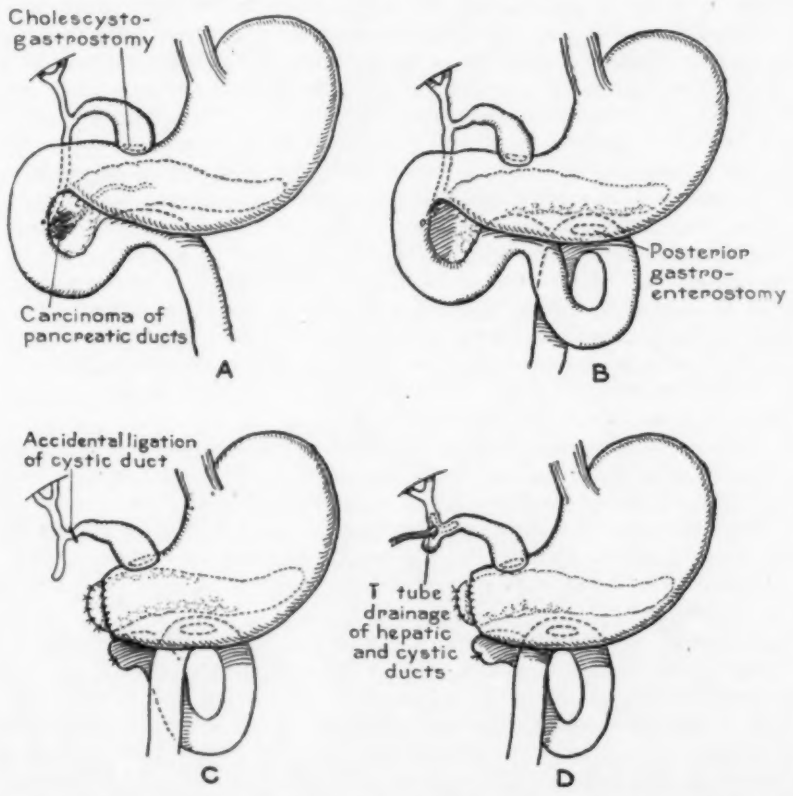

Fig. 1 (case 1).—Pancreaticoduodenal resection for cancer arising in pancreatic duct. *A*, cholecystogastrostomy *B*, posterior gastroenterostomy; *C*, pancreaticoduodenal resection, with accidental ligation of the cystic duct; *D*, T tube drainage of common, hepatic and cystic ducts.

the pancreas. The duodenum was then severed by the cautery between clamps. The blind end was closed in the routine manner, three layers of sutures being used. Dissection was continued in order to mobilize the duodenum further, and it was again severed in the same manner as before. About 4 inches (10 cm.) of duodenum was thus freed and excised. The pancreas was incised about 3 cm. distal to the palpated tumor. Both pancreatic ducts were ligated with silk (fig. 1*C*). The wound was closed in layers with silk and reenforced with dermal stay sutures.

After the patient was returned to his room, it was realized that an operative error had been made. During the third phase of the operation, the common duct and the pancreatic ducts were ligated. At this time a traction suture of chromic surgical gut had been placed around the cystic duct in order to make the distended common bile duct more prominent to help to distinguish it from the portal vein, which was extremely large and in close approximation and which was dissected free with considerable difficulty. When the vessels, ducts and bleeding point were all ligated, the traction suture was inadvertently tied instead of being removed. The patient, therefore, was returned to the operating room, and after basal anesthesia was induced with tribromoethanol the upper portion of the wound was opened to expose the cystic and common bile ducts. Both stumps were picked up, and the ligatures around the end of the common duct and the inadvertently tied guy ligature around the cystic duct were removed. The patency of the cystic duct was determined by probing, and the juncture of the two ducts was then opened to facilitate placement of a T tube into both (fig. 1*D*). The ducts were repaired with fine silk sutures and the wound closed with through and through sutures.

The pathologic report was as follows: "The length of the duodenum is about 10 cm. and that of the common bile duct 6 cm. It is ligated at its upper extremity. The portion of pancreas lying in the curve of the duodenum measures 5 cm. in its greatest extension. The duodenal mucosa is normal. There is no anatomic stricture of the common duct. The pancreatic duct probes through to the duodenum without obstruction. The inferior portion of the pancreas just adjacent to the common duct has lost its normal lobulation, is firm, not extremely hard and rather grayish yellow in color, and it presents small areas of necrosis and fine yellow streaking. The palpable area of the induration in the head covers an area of about 2 by 1.5 by 1.5 cm."

The microscopic report read: "This is a low grade adenocarcinoma of major pancreatic ducts and their branches associated with extreme interstitial fibrosing pancreatitis. There is papillary duct overgrowth, with excess mucin production, distention of ducts and atypical nuclear changes. There is parenchymatous regenerative proliferation. Despite the low grade, this type of lesion is known to metastasize. The lymph node embedded in the pancreas near to the lesion itself fails to show tumor."

The early postoperative course was good in view of the magnitude of the procedure and the unusual complication. The temperature was 104 F. on the first postoperative day, but the daily spikes gradually subsided and it ranged up to 101 F. by the tenth postoperative day. Biliary drainage, as well as drainage from the wound itself, gradually increased, and the net amout from both sources ranged from 1,600 cc. to 2,300 cc., reaching that amount by the fifteenth postoperative day. The material was returned to the patient through a Levine tube. On the twenty-third postoperative day the T tube was removed, and biliary drainage was then even more profuse. The patient became extremely weak, and even slight exertion caused weakness and profuse sweating. He collapsed while going to the bathroom on one occasion, and on the following day laboratory studies showed an icteric index of 10, a blood sugar content of 50 mg. per hundred cubic centimeters and a blood urea nitrogen level of 62 mg. It was wondered if the patient might have had a hypoglycemic reaction at the time he fainted. The drainage gradually decreased and there was pigmentation in the stool, so that the cholecystogastrostomy opening was assumed to be patent.

Despite all supportive measures the patient became weaker, though he was ambulatory. He was discharged on July 3, eighty-two days after his first operation. He died on July 22, one hundred and two days after his first operation.

Comment.—The resection in this case was performed in three stages because it was feared that the patient's condition would not permit lengthy procedures. His remarkable endurance and capacity in the third and fourth operations were due, no doubt, to the recuperation after relief of the biliary obstruction in the first operation. The large volume of secretion indicates that a pancreatic fistula was present also, though activation of the ferments never occurred to produce excoriation of the skin.

CASE 2.—M. P., a 39 year old single registered nurse, was admitted to the Memorial Hospital on April 8, 1940, complaining of jaundice of about three months' duration, though itching had preceded the onset of icterus by one month. Three weeks after the onset of jaundice, diarrhea had developed. Though the stools were pigmented, they were light and grayish yellow. Her physician prescribed bicarbonate of soda and zilatone, which she took without obtaining relief. Her skin became extremely dry, and pruritus was marked. While she had no pain, she did have tenderness in the right upper abdominal quadrant. Milk, cream and fats produced discomfort and nausea, so that she omitted them from her diet. She had never suffered a qualitative dyspepsia before the present illness. She had not vomited, but she had lost 15 pounds (6.8 Kg.).

Physical examination revealed a slender woman, weighing 120 pounds (54 Kg.). There was a mild degree of jaundice. In the right upper quadrant of the abdomen there were tenderness and muscle tenseness, but no mass could be palpated.

Laboratory studies showed a hemoglobin content of 55 per cent, a red blood cell count of 2,912,000, a white blood cell count of 12,900, with 86 per cent segmented neurophils and a serum bilirubin content of 9 mg. per hundred cubic centimeters. The bleeding time was one minute and ten seconds and the clotting time two minutes and fifteen seconds. Bile was present in the urine.

Cholecystography failed to reveal a gallbladder shadow, and no evidence of opaque biliary calculi could be seen.

On April 9, 1940, a laparotomy was done through a right rectus incision after a diagnosis of acute exacerbation of chronic cholecystitis, with cholelithiasis and questionable choledocholithiasis, had been made. Spinal anesthesia was used. An enormously dilated biliary tract and gallbladder were found, the common duct measuring 2 cm. in diameter. By freeing the duodenum by Kocher's maneuver, a small mass measuring 1.5 cm. in diameter could be palpated from the posterior side of the duodenum in the region of the papilla of Vater. A diagnosis of cancer was made. Gastrojejunostomy and cholecystogastrostomy were performed as shown in figure 2*A*. Closure was effected with layers of silk without difficulty.

The postoperative course was complicated by pain in the right upper abdominal quadrant and tenderness on the eighth postoperative day. It was felt that there was a leak in one of the suture lines, but with conservative therapy all complications, including the jaundice, subsided. A small hematoma of the wound evacuated spontaneously, and culture revealed alpha hemolytic streptococci as the infecting bacteria.

On May 3, 1940, twenty-four days after the first procedure, a transverse incision was made in the upper abdominal area, with the patient under spinal anesthesia induced by "nupercaine." The areas of both previous anastomoses were well healed, though considerable adhesions were found around the cholecystogastrostomy opening. The pyloric antrum was transected between Payr clamps,

the duodenum and the head of the pancreas mobilized and the third portion of the duodenum sectioned between Kocher clamps and closed with Parker-Kerr technic. The head of the pancreas was transected and the common duct freed, cut, clamped and doubly ligated. The duct of Wirsung was ligated and the head of the pancreas closed with mattress sutures (fig. 2*B*). The stomach was closed by the Parker-Kerr technic and the usual layer closure of the laparotomy wound done, with drainage to the site of the transected head of the pancreas. The postoperative course was complicated by the presence of a small pancreatic fistula.

Pathologic examination revealed a soft cauliflower-like papillary tumor (fig. 3) which measured 2.5 cm. in diameter and was elevated 1 cm. above the mucosa. The pancreatic duct passed through the center of the tumor, without any

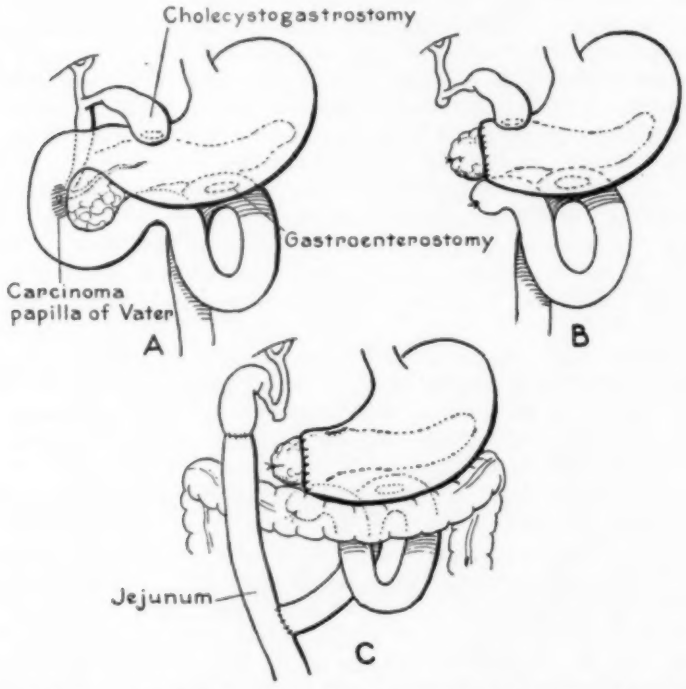

Fig. 2 (case 2).—Pancreaticoduodenal resection for cancer of peripapillary origin. *A*, cholecystogastrostomy and posterior gastroenterostomy; *B*, pancreaticoduodenal resection; *C*, revision of biliary-intestinal anastomosis, with cholecystojejunostomy and Roux jejunojejunostomy.

obstruction being evident when it was probed. One lymph node was present and appeared to be involved by metastatic tumor.

Microscopic examination revealed a grade II malignant adenoma of the intestinal type, associated with chronic interstitial and glandular pancreatitis, with atrophy and suppuration in and about the ducts. The node showed no evidence of tumor.

The postoperative course was complicated by an infection of the urinary tract and by a pancreatic sinus which did not excoriate the skin and drained little. The patient was discharged on the forty-ninth postoperative day. About five months later the sinus closed.

In January of 1941 the patient was admitted for metabolic studies, but because she had been taking liver and yeast the studies were delayed until April. She then stated that shortly after the preceding admission she noticed a clay-colored stool and that soon thereafter chills, nausea and vomiting, but no pain had developed. This passed away without treatment in three or four days. Since that time she had had six to eight gray formed soft stools daily and a loss of weight of 15 pounds (6.8 Kg.). The studies at that time were the subject of a special report by

Fig. 3 (case 2).—Photograph of resected specimen, showing soft cauliflower-like tumor measuring 2.5 cm. in diameter.

Rekers, Pack and Rhoads.[36] It was shown that the administration of large quantities of pancreatic enzymes was followed by conspicuous clinical benefit and by a significant decrease in the amounts of fat and nitrogen excreted in the feces. An increase in the protein content of the diet resulted in increased absorption of fat. An increase of fat content of the diet resulted in an increase of fat absorbed but in no lessening of the amount of fat lost.

36. Rekers, P. E.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: V. Pancreatic Insufficiency in a Patient Treated Surgically for Carcinoma of the Ampulla of Vater, J. A. M. A. **122**:1243-1245 (Aug. 28) 1943.

On Aug. 20, 1941, the patient noticed abdominal fulness, belching and epigastric distress, followed in a few hours by chills and fever. The next day jaundice was obvious and the serum bilirubin content was 2.5 mg. per hundred cubic centimeters. A diagnosis of cholangitis was made. A mass was then palpable in the right epigastric region. Chills and fever continued despite sulfadiazine therapy, and two weeks after the patient's admission, on September 2, a blood culture showed Streptococcus viridans. The same was shown on September 6, but after that no cultures of the organism could be obtained, and she was discharged to her home. Recurrent febrile episodes terminated in her return to the hospital on Feb. 11, 1942, suffering from another attack. The serum bilirubin content was 5 mg. per hundred cubic centimeters.

On Feb. 18, 1942, the patient was operated on again. Many adhesions were found around the gallbladder. The stoma of the cholecystogastrostomy measured approximately 2 mm. When the anastomosis was freed with a rim of the stomach, it was found that the stoma could easily be dilated to release thick green inspissated bile. The gallbladder itself was filled with many small calculi, none over 5 mm. in diameter. The pancreas was small and fibrotic, and no evidence of residual cancer was found. The liver was dark and slightly enlarged, and after the gallbladder was drained it seemed to decrease visibly in size. An antiperistaltic cholecystojejunostomy, with a closed loop and a Roux anastomosis, was effected to restore gastrointestinal continuity (fig. 2*C*).

Postoperative nutrition was maintained by an orojejunal tube, and recovery was uneventful. The patient was discharged on the twentieth postoperative day after a relatively afebrile course.

After her return home, intermittent jaundice, chills and fever continued. One year later, on March 19, 1943, she was admitted to the hospital for the seventh time because of daily chills and a temperature which ranged from 103 to 105 F. The serum bilirubin content was 8.1 mg. per hundred cubic centimeters and the prothrombin time 51 per cent of normal. The serum cholesterol was 183 mg. per hundred cubic centimeters, with 116 mg. of free and 67 mg. of esterified cholesterol. The alkaline phosphatase was 33.8 units. Total protein was 7.5 mg. per hundred cubic centimeters. Under sulfanilamide therapy the temperature subsided, but the patient was told that if symptoms recurred she was to undergo another operation for exploration of the common hepatic duct and for removal of the stones which had probably reformed in it. It was proposed to do a choledochojejunostomy to give adequate biliary drainage and to prevent stasis. The patient returned to her home and was not heard from again until a letter told of her death on May 23, 1943, six weeks after her last hospitalization. She had survived thirty-six months after her first operation and forty months after the onset of symptoms.

Comment.—This patient presented a picture which is not unusual after the original operation of Whipple, Parsons and Mullins has been performed. In a study of 4 patients on whom this operation had been performed, Whipple found that cholangitis of varying severity developed sooner or later. He described the findings at autopsy on the first patient who had been subjected to the operation. The patient had died eight months postoperatively of acute cholangitis with multiple abscesses of the liver. He felt that the cause was probably the injection of gastric contents contaminated by the jejunum into the gallbladder, with retention of the infectious material in the gallbladder as a result of the inflammatory

edema of the cholecystogastrostomy stoma, or gastric contractions closing the stoma. The biliary-intestinal anastomosis, therefore, was reconstructed in accordance with the operation described by Whipple[37] in 1938, an antiperistaltic cholecystojejunostomy and a Roux jejunojejunostomy being performed. In retrospect, there is little doubt that the edematous, thick, and chronically infected gallbladder wall again contracted and prevented free biliary drainage, which might have been avoided by the use of the common duct itself in the anastomosis.

The patient, however, showed no recurrence of the lesion at the time of the last operation, twenty-one months after the initial procedure, and she survived for three years after the operation and for forty months after the onset of symptoms of obstructive jaundice.

CASE 3.—J. C., a 45 year old Jewish man, was admitted to the Memorial Hospital on Nov. 7, 1945. About two and one-half years before he had noticed loss of appetite, heartburn and pains after meals. There was no qualitative dyspepsia. Itching and icterus soon developed, and he was told that he had jaundice. He was given rest in bed and a high carbohydrate diet for five months. After that he was without complaints, and his weight was 165 pounds (74 Kg.). In February 1944 jaundice and pruritus recurred. A series of roentgenograms of the gallbladder was said to show gallstones. On March 8, 1944, a laparotomy was done in another hospital; the preoperative diagnosis was obstructive jaundice. The report was as follows: "There is an enlarged gallbladder, about two and one-half times the normal size and with moderately edematous walls. No calculi were present The common duct was moderately dilated, and no calculi were found. The head of the pancreas was enlarged, nodular and firm."

A biopsy of material from the pancreas was done and a cholecystostomy performed. The report of the biopsy was as follows: "In portions of these sections of the pancreas there is a marked increase of the connective tissue. The acini are atrophied. Some of the ducts are dilated. The diagnosis is chronic pancreatitis."

The patient was hospitalized for three weeks. The biliary fistula drained for four months and then was closed for two days; after a mass rapidly formed the wound broke down and drained as another fistula. The icteric index was 70, and the van den Bergh test showed an immediate direct reaction. He was operated on again on Aug. 14, 1945, a cholecystogastrostomy being performed. At this time the surgeon commented on the fact that the cancer involved not only the head of the pancreas but almost the entire organ.

After returning home, the patient again noticed loss of appetite and weight. On one occasion he had tarry stools which contained some bright red blood. He then became constipated and required enemas. Heartburn, gas pains, nausea and vomiting and "acid eructation" had recurred before he was admitted to our hospital.

Physical examination revealed a well developed man of 45 who was somewhat emaciated. His abdomen was moderately distended, with the scar from a McBurney incision and one in the right upper abdominal quadrant. The liver was palpable 2.5 cm. below the costal margin, and it was smooth.

Laboratory studies revealed a hemoglobin content of 47 per cent, a red blood cell count of 2,300,000 and a white blood cell count of 8,000, with a normal dif-

37. Whipple, A. O.: Surgical Treatment of Carcinoma of the Ampullary Region and Head of the Pancreas, Am. J. Surg. **40**:260-263, 1938.

ferential count. The prothrombin time was 88 per cent of normal. The serum bilirubin was 0.7 mg. per hundred cubic centimeters and the serum chlorides 97 milliequivalents. The total serum cholesterol was 143 mg., with a normal relationship of free and esterified forms, the serum proteins 7.1 Gm. and the blood sugar 119 mg. per hundred cubic centimeters. The serum amylase was 167 units. The glucose tolerance curve was flat, indicating impaired absorption.

Gastric retention of over a liter of fluid necessitated frequent aspiration and lavages and contributed to a weight loss of 6 pounds (2.6 Kg.) in six days in the hospital.

A series of gastrointestinal roentgenograms revealed poor tone, with an increased capacity. An area of angulation and fixation was noted along the lesser

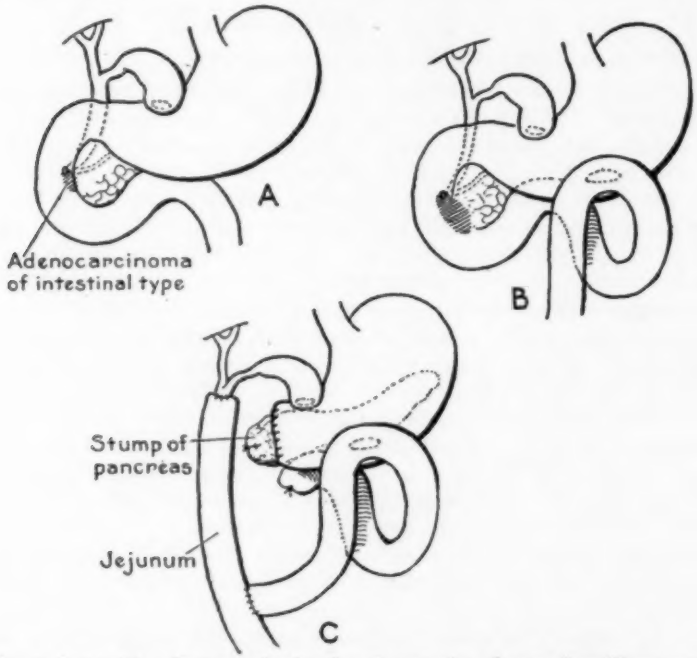

Fig. 4 (case 3).—Pancreaticoduodenal resection for peripapillary cancer. *A*, cholecystogastrostomy; *B*, anterior gastrojejunostomy; *C*, pancreaticoduodenal resection, with choledochojejunostomy and Roux anastomosis. The last operation was done two and one-half years after the onset of symptoms.

curvature, which was due to the cholecystogastrostomy. The duodenal loop, though difficult to observe, seemed normal. The visualization of the gallbladder was of no value except that it showed a distention of the biliary radicles.

After six days of gastric lavage and aspiration, the gastrointestinal roentgenograms were again taken. A deep epigastric mass could be felt, and it was associated with an area of narrowing in the descending portion of the duodenum just distal to the bulb. It also appeared that the stomach might be associated with the mass at its point of fixation. The patient was considered to have a tumor involving the second portion of the duodenum. After seven transfusions of blood, the hemoglobin value was 83 per cent, the red blood cell count 4,200,000 and the white blood cell count 12,600. However, the serum bilirubin level rose to 2.9 mg. per hundred cubic centimeters and the serum chloride content fell to 72 milliequivalents, with

an increase of the blood urea nitrogen to 39 mg. per hundred cubic centimeters. When these were brought to normal levels, Dr. John Pierson did an exploratory laparotomy (Nov. 26, 1945) through a transverse incision in the upper abdominal area, continuous spinal anesthesia being used. A nodular mass was palpated in the head of the pancreas which was estimated to be 6 by 6 cm. The head of the pancreas was movable on the posterior wall of the abdomen (fig. 4*A*). It was concluded that the mass was resectable and a two stage resection was planned. An antecolic gastrojejunostomy was performed (fig. 4*B*). The postoperative course was not remarkable save for mild hypoproteinemia and a slight infection of the wound. The patient was discharged on his twenty-second postoperative day.

On January 20, one month later, he was readmitted to the hospital. A significant change since his discharge was present in the form of profound anemia, the red blood cell count being 2,400,000, the hemoglobin content 46 per cent (Sahli) and the white blood cell count 8,200. Five transfusions of 500 cc. each brought the red blood cell count to 3,600,000, with 69 per cent hemoglobin, on the day his last operation was performed (Feb. 6, 1946). With the use of continuous spinal anesthesia, the abdomen was entered through a transverse incision between the costal margins. Exploration revealed numerous and troublesome old postoperative adhesions, a well functioning cholecystogastrostomy opening and an anterior gastrojejunostomy opening. A mass measuring 10 by 7 by 5 cm. was found in the region of the head of the pancreas. It appeared to arise in the second portion of the duodenum and to extend into the head of the pancreas. The liver was not enlarged, and no palpable lymph nodes precluded operation.

Accordingly, radical resection was undertaken by severing the stomach distal to the site of the gastroenterostomy, the DePetz mechanism being used, with subsequent inversion of the stapled end in two layers. The common bile duct was divided at the level of the junction of cystic and common ducts, and the tumor mass together with the head of the pancreas and the duodenum up to the fourth part was removed en bloc. The duodenal stump was closed in three layers and a Roux type of jejunojejunostomy and an end to end choledochojejunostomy performed. The main and pancreatic ducts were separately ligated (fig. 4*C*). The wound was drained through a stab wound in the right flank, two Penrose drains being carried to the stump of the duodenum. One drain from the inverted stump of the pancreas was brought through the right margin of the wound. Layer closure of the wound was done with silk sutures and bolstered with silk retention sutures.

Pathologic examination revealed considerable extension of the growth, and while the serosa was not altered the mucous membrane was replaced in the central segment by an irregular, ulcerating, nodular tumor surface which extended to the line of section distally. The lesion had infiltrated the duodenal wall and the head of the pancreas. The common duct could be identified only in cross section. The microscopic report was "adenocarcinoma, grade III, of intestinal origin, metastatic to one node, and invading the pancreas."

Wangensteen suction was maintained for three days, and then feedings with an orojejunal tube were begun. A small amount of biliary drainage began from the drainage site of the stab wound on the fourth postoperative day. Biliary drainage increased, and by the ninth postoperative day 720 cc. was collected. The amount rapidly decreased thereafter. The weight loss from the date of admission up to the thirteenth postoperative day was 5 pounds (2.3 Kg.), and by the fourteenth postoperative day the wound was healed and there was no more drainage.

The patient was discharged on March 13, his thirty-fifth postoperative day, at which time he manifested no sign of pancreatic insufficiency. On a diet of 150

Gm. of protein, 80 Gm. of fat and 200 Gm. of carbohydrate, he excreted only 1.5 to 2 Gm. of fecal nitrogen per day and only 3 to 6 Gm. of fat. The serum amylase was 120 units, the hemoglobin content 90 per cent, the red blood cell count 4,400,000 and the white blood cell, 4,700.

After his discharge from the hospital hypochromic anemia developed, and on May 7 the red blood cell count was 4,790,000, with 75 per cent hemoglobin. This was corrected with iron therapy, and by May 22 his hemoglobin content was 100 per cent and the red blood cell count 4,910,000.

On June 10, the patient was again admitted to the hospital complaining of onset of pain in the right upper abdominal quadrant twenty-four hours before. The pain was continuous but varied in intensity. He felt weak but had no nausea or vomiting. He had had no bowel movement since just before the onset of the illness. He was found to have pneumonia, and he recovered rapidly after appropriate treatment.

He was last examined in March 1947, at which time there was no evidence of recurrence of his disease. He was then under treatment for a ureteral stone.

Comment.—This case illustrates a long stage of grace in resectability. Despite previous explorations, the tumor was resectable over two and one-half years after the onset of initial symptoms. The difficulty in obtaining material for a satisfactory biopsy was not unusual. It is most interesting to note that despite permanent occlusion of both pancreatic ducts the patient presented no signs of pancreatic insufficiency. He has survived for over four years since the onset of symptoms and for twenty-one months after resection of a grade II adenocarcinoma with metastasis to the lymph nodes, and he now shows no signs of recurrent cancer.

Case. 4.—S. H., a 31 year old naval ensign, was admitted to the gastric service of Memorial Hospital on Dec. 21, 1945, with the chief complaint of epigastric pain. This had been present for thirteen months. The onset, in November of 1944, was associated with frequent black stools, relieved by dietary management. Five months later, on March 5, 1945, he again suffered severe melena. On March 21, he was admitted as a patient on a hospital ship because of the intestinal hemorrhages. It was noted that he not only was "bled out" but also seemed jaundiced. He was given thirteen blood transfusions. A series of gastrointestinal roentgenograms showed a defect in the mid-portion of the duodenum (fig. 5). He was therefore transferred to the Norfolk Hospital in the United States on June 27, 1945. He was feeling well again except for slight epigastric discomfort, but gastrointestinal roentgenograms showed a constant irregularity of the descending loop of the duodenum, with narrowing and an apparent filling defect but no obstruction. He was considered to have a peptic ulcer and was placed on a Sippy regimen. By August 11 he had been asymptomatic for so long that he was sent to limited duty. In late August he again became jaundiced, and on September 4 he was admitted to another hospital for acute infectious jaundice. His icteric index was 42.7, and the van den Bergh reaction was read as direct immediate. His stools were clay colored, and there was occult blood present. By September 24 the icteric index was 64.2, and the diagnosis was changed to obstructive jaundice. An exploratory laparotomy on October 3 revealed an enormously distended gallbladder and common duct. No ulcer could be felt in the stomach or duodenum. The head of the pancreas was the size of a small orange and was hard and nodular. Carcinoma was thought to be present, and material for a biopsy was taken. A cholecystoje-

junostomy was done. The report of the biopsy stated that the material contained pancreatic tissue with normal acini. Scarring and lymphocytic infiltration were present, but there was no evidence of cancer. On the second postoperative day the icteric index was 93.7. The subsequent course was satisfactory, and by October 27 the icteric index was 17.

On November 13 another series of gastrointestinal roentgenograms was made. This series also showed a constant filling defect of the mid-portion of the duodenum, with slight spreading of the loop. It was thought that the size of the de-

Fig. 5 (case 4).—Preoperative gastrointestinal roentgenogram, showing constricting defect in the descending loop of the duodenum.

fect had increased. The diagnosis of carcinoma of the duodenum in the region of the ampulla of Vater was made. The patient was transferred to the Brooklyn Naval Hospital and thence to the Memorial Hospital.

Physical examination revealed a well proportioned young white man. He was 75 inches (190.5 cm.) tall and weighed 191½ pounds (87 Kg.). He appeared to be in good health. There was no evidence of jaundice. The only significant physical findings were a healed scar from a McBurney incision and an oblique scar in the right upper abdominal quadrant. There was tenderness beneath the scar, but no mass could be felt.

Fig. 6. (case 4).—Gastrointestinal roentgenogram after cholecystojejunostomy, showing the persisting filling defect in the descending portion of the duodenum and the functioning cholecystojejunal anastomosis.

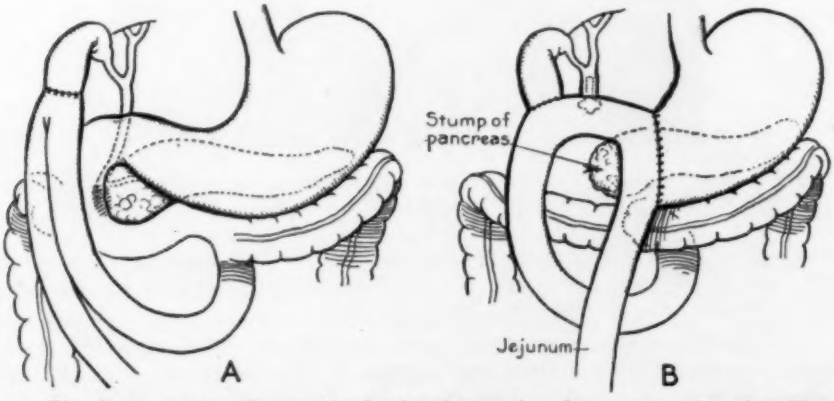

Fig. 7 (case 4).—Pancreaticoduodenal resection for cancer of peripapillary origin. *A*, first procedure in a loop cholecystojejunostomy; *B*, resection, with choledochojejunostomy and terminolateral gastrojejunostomy.

The blood count revealed a hemoglobin content of 85 per cent (Sahli), a red blood cell count of 4,300,000 and a white blood cell count of 7,400 with 80 per cent filamented neutrophils and 20 per cent lymphocytes. The hematocrit value was 50 per cent and the mean cell volume 120 cubic microns. The prothrombin time was 73 per cent of normal. Total cholesterol was 249 mg. per hundred cubic centimeters, the free cholesterol being 82 mg. and the cholesterol esters 167 mg., and the alkaline phosphatase 4.1 Bodansky units. The serum calcium was 10.2 mg., inorganic phosphorus 3.36 mg., serum protein 6.5 Gm., fibrinogen 300 mg. and serum bilirubin 1.5 mg. per hundred cubic centimeters.

A series of gastrointestinal roentgenograms revealed a fusiform constriction, 1½ inches (4 cm.) long, in the mid-portion of the descending duodenum. It was felt that this might represent duodenal constriction due to an aberrant annular pancreas. Roentenograms made after a barium enema and roentgenograms of the chest showed no abnormality (fig. 6).

Dr. Jules Abels and Dr. Frederick Homburger then outlined metabolic studies to determine the degree of the patient's pancreatic dysfunction, and it was shown that there was positive nitrogen balance and that there was no steatorrhea.

On Jan. 4, 1946, the patient was operated on under continuous spinal anesthesia. A transverse incision was made, extending between the tips of the ninth costal cartilages. A firm mass measuring 10 by 10 by 8 cm. was found in the region of the second portion of the duodenum, extending to the juncture of the second and third portions. The mass seemed to be intraluminal at one side and infiltrating the head of the pancreas on the other. The cholecystojejunostomy wound seemed well healed, and no evidence of spread or of metastasis to the liver was found (fig. 7*A*).

The distal end of the stomach, the duodenum and the head of the pancreas were mobilized. The stomach was transected between the middle and distal thirds after it had been clamped with the DePetz mechanism. The duodenum was divided between Kocher clamps at the distal end of the third portion and the distal end closed in three layers by the Parker-Kerr technic. Then the tumor mass was freed completely; the bile ducts were freed, clamped and transected just below the entrance of the cystic duct, and most of the head of the pancreas was resected. The duct of Wirsung was ligated and suture transfixed before the capsule over the remaining portion of the head of the pancreas was invaginated. An antecolic, end to side, oralis totalis gastrojejunostomy was performed, the proximal loop being anastomosed to the lesser curvature of the stomach, and a choledochojejunostomy was performed just distal to the site of the cholecystojejunostomy. The anastomosis was made over a Pezzer catheter, great attention being paid to obtaining mucosal apposition (fig. 7*B*). A Penrose drain was placed to the duodenal stump and one in the right paracolic gutter. They were brought out through a lateral stab wound. Layer closure with interrupted fine silk with sutures was done, with figure-of-eight retention sutures. During the operation, 2,200 cc. of blood was given. The patient's postoperative condition was excellent.

The specimen is shown in figure 8*A*. The pathologic report read as follows: "When the duodenum was opened, it was found that a tumor measuring 7 cm. in greatest diameter arose in the region of the caruncle major. Careful dissection through the external part of the specimen failed to reveal the common bile duct, though Wirsung's duct was identifiable. When the duct of Wirsung was probed, it was shown that the ampulla of Vater was occupied by grayish white firm tumor tissue, which on cut section appears to be limited to the muscular layer of the duodenum. The proximal end of the duodenum is about 1.5 cm. from the borders of the ulcerated tumor." Two lymph nodes were found in the specimen, neither showing gross involvement.

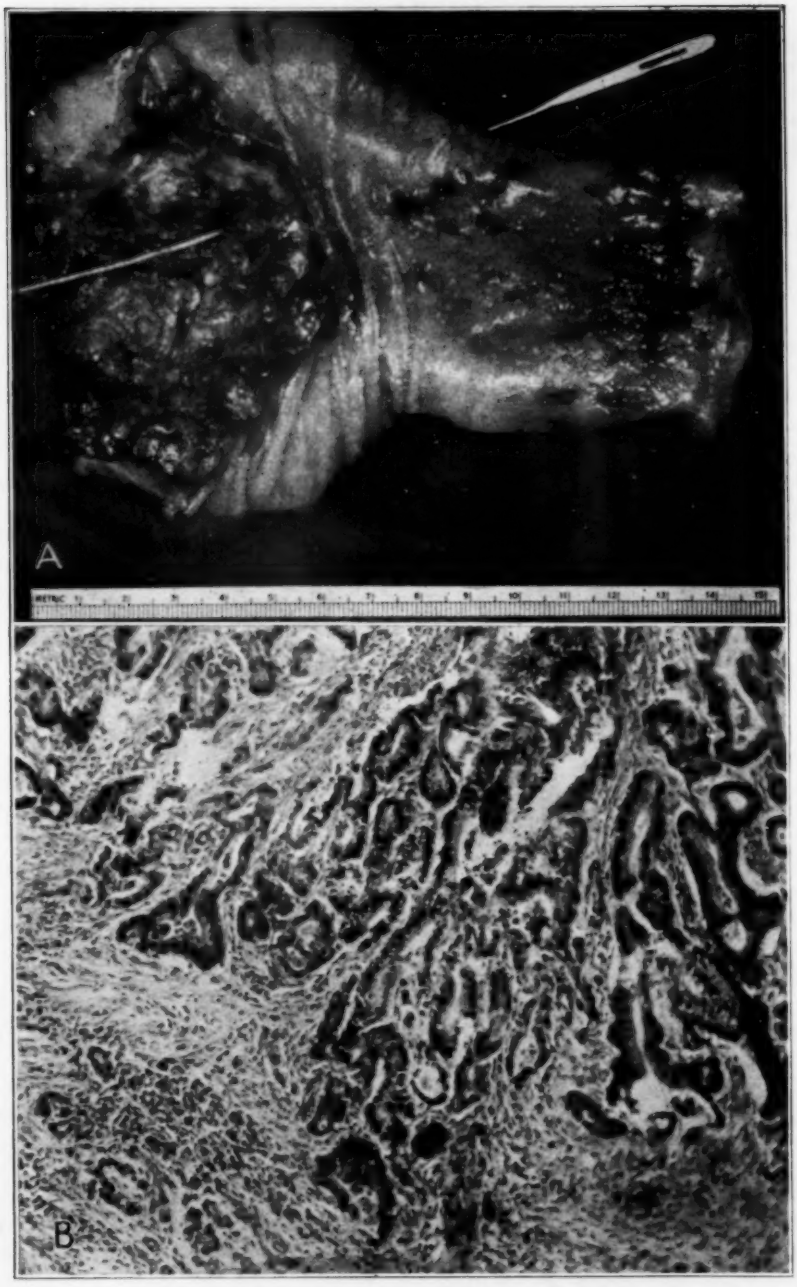

Fig. 8 (case 4).—*A*, photograph of gross specimen, showing the tumor arising in the region of the caruncle major. The probe is in the duct of Wirsung. *B*, photomicrograph showing an adenocarcinoma of intestinal origin and of grade II histologic malignancy; × 240.

Microscopic examination revealed an adenocarcinoma of grade II malignancy, of intestinal origin, with infiltration of the pancreas (fig. 8*B*). There was no evidence of tumor at the transection site of the pancreas, and the nodes were free from metastasis.

The postoperative course was not unusual. Wangensteen suction was employed. The maximum temperature was 101.6 F (by rectum), on the fourth postoperative day, though 1,230,000 units of penicillin were given in the first postoperative week. The patient was afebrile after the tenth postoperative day. The serum protein level was below normal on two occasions of the third and fourth

Fig. 9 (case 4).—Postoperative gastrointestinal roentgenogram showing reflux of barium into the afferent loop, demonstrating the need for a longer loop between the biliary-intestinal and the gastrointestinal anastomosis.

postoperative days, the lowest being 5.5 Gm. per hundred cubic centimeters. This was corrected by transfusions of blood and by administration of "amigen" both intravenously and by mouth.

Aside from the metabolic aberrations subsequent to loss of external pancreatic enzymes, the only complication was the establishment of a pancreatic fistula on the thirty-seventh postoperative day. For the thirty-six hours preceding this there was pain in the central abdominal area, with a little yellow discharge from the drainage site but no febrile reaction. Then there was a copious white clear discharge with a

silk ligature in it, after which there was immediate and complete relief. The patient suffered no excoriation of the skin from this, and therefore there was no activation of the trypsinogen in the secretion.

Postoperative metabolic studies were carried on by Dr. Rhoads and Dr. Homburger,[38] and the patient spent a postoperative period of forty-seven days in the hospital. By the fifth postoperative day the stools were pasty and large, thus manifesting pancreatic insufficiency. It was found that administration of pancreatin in large amounts finally enabled the patient to utilize a fairly normal diet. The preoperative excretion of fat was not determined, but after the operation the amount in the stool was around 10 Gm. in spite of the complete absence of fat in the diet. It could be maintained at this level, after the addition of dietary fat, by the use of pancreatin. Addition of steapsin (a lipase preparation of higher lipolytic activity than pancreatin in vitro) did not reduce excretion of fat in the stool. It appeared that the patient's metabolic disturbance was satisfactorily controlled and that he would be able to get get along on a fairly normal diet (approximately 275 Gm. of carbohydrate, 171 Gm. of protein and 75 Gm. of fat with 15 Gm. of "panteric" [triple strength pancreatin] per day).

In October 1946 the patient noticed gradual development of an abdominal mass which occasioned a little pain but did not interfere with his good appetite. It gradually reddened, and he was admitted to the hospital for incision and drainage. Subsequently, another abscess at the superior pole of his first incision opened spontaneously, but a large tender mass was still palpable deep in the epigastrium. It extended to the navel. A series of gastrointestinal roentgenograms (fig. 9) showed a mass behind the stomach. There was a delay in emptying in the efferent loop and there was a reflux of barium to the line of the biliary anastomosis in the proximal loop. The mass was considered to be recurrent carcinoma. Because of Pack and McNeer's[39] experience with palliative high voltage roentgen therapy in cases of pancreatic cancer, treatment was begun on November 10 using 1,000 kilovolts, 3 milliamperes, 2 mm. of mercury, 2 mm. tungsten, an 8 mm. copper filter and a 70 cm. target skin distance through an 18.5 by 18.5 cm. port, daily fractions of 250 r being given until a total of 4,000 r were delivered. At the time we last examined the patient, there was little reaction of the skin, but the mass had definitely decreased in size. About one month after his last roentgen treatment and after he had returned home, pain in the right upper abdominal area recurred, associated with considerable discharge from the previous drainage sites. About eight weeks after his last treatment, surgical exploration was done in his home city. A rigid-walled cavity was found beneath the liver, and the carcinoma was recurrent in the entire upper part of the abdomen. In early April of 1947 his condition was considered terminal, sixteen months after resection of the cancer and twenty-nine months after the onset of symptoms.

Comment.—Despite the degree of histologic malignancy of grade II and the direct extension into the pancreas, no nodes were involved in this case and the cancer was resectable. Again the difficulty in obtaining material from these lesions for biopsy is seen. All of the last 3 patients presented intense secondary anemia which was the result of the duodenal ulceration. If a functioning cholesystostomy opening had not been pres-

38. Rhoads, C. P., and Homburger, F.: Unpublished data.

39. Pack, G. T., and McNeer, G.: Radiation Treatment of Pancreatic Cancer, Am. J. Roentgenol. **40**:708-714, 1938.

ent, a longer loop of jejunum would have been used between the choledochojejunostomy sites, which we now deem highly desirable. The roentgenologic studies show that the afferent loop is not defunctionalized when a short loop is used, and we are aware that the absence of fever does not preclude asymptomatic and unsuspected ascending cholangitis, as has been recently described by Zazlow and Counseller,[40] which may have been a complicating factor in this case. Cole and Reynolds have reported a procedure in which a long loop of jejunum is used. It seems as satisfactory as any operation described to date and has an advantage in that the biliary anastomosis in which the long loop is used can be effected first if an operation becomes necessary because of a sudden change in the patient's condition, and as much freedom is permissible at the subsequent procedure as in any other type of operation. The procedure approaches the ideal in that it necessitates only two anastomoses, leaves a long defunctionalized loop of jejunum proximal to the gastroenteric stoma for biliary anastomosis and also lends itself readily to the performance of pancreaticojejunostomy if such is desired. If two stages are necessary, choledochojejunostomy should be performed at the second operation since the anastomosis between the gallbladder and the jejunum may not remain intact. The use of this type of biliary anastomosis has been recently described by Brunschwig.[41]

Case 5.—S. Z., a 70 year old Jewish man, was admitted to the hospital on April 20, 1946. He said he had been perfectly well until two weeks before, when his skin began to turn yellow. He had slight anorexia associated with this but no loss of weight, epigastric pain, nausea or vomiting. There had been no acholic, bloody or tarry stools and no diarrhea. About the day before his admission his skin began to itch.

Physical examination revealed a well nourished but highly jaundiced man who apparently was in no distress. His abdomen was soft. The gallbladder was distended and easily palpable, but the liver and the spleen could not be felt. He had a greatly hypertrophied prostate. His weight was 165 pounds (75 Kg.).

Laboratory studies revealed 14.1 Gm. of hemoglobin per hundred cubic centimeters (94 per cent by the Sahli determination), a red blood cell count of 4,460,000 and a white blood cell count of 8,300. The blood urea nitrogen was 11.1 mg. per hundred cubic centimeters and the total cholesterol 225 mg., with 76 mg. in the free form. The urine was not remarkable save that it gave a positive reaction in a 1:20 dilution to the Wallace-Diamond test for urobilinogen. The stool contained urobilinogen but no blood.

The series of gastrointestinal roentgenograms was reported to show large rugae in the fundus, with increased tone and peristalsis. The duodenal bulb was only partly filled and was small. It was assumed to be spastic in nature, but

40. Zazlow, J., and Counseller, V. S.: Suppurative Cholangitis Complicating Sidetracking Operations of the Biliary Tract: Report of a Case, Proc. Staff Meet., Mayo Clin. **21**:241-246, 1946.

41. Brunschwig, A., and Tiholiz, I. C.: Surgical Treatment of Malignant Tumors of the Duodenum Exclusive of Those Arising from the Papilla of Vater, S. Clin. North America **26**:163-175, 1946.

whether this was secondary to pyloric spasm or to a duodenal lesion could not be ascertained. There was no residue in the stomach after three hours. Reexamination after dietetic and antispasmodic therapy was requested. On the day following admission the patient had a temperature of 104 F., a pulse rate of 104 and a respiratory rate of 36 per minute. His white blood cell count was 17,400, with 89 per cent neutrophils. The serum bilirubin then was 23.1 mg. per hundred cubic centimeters and the total protein 6.21 Gm., with 3.30 Gm. of albumin and 2.91 Gm. of globulin. The prothrombin time was 29.4 seconds (normal, 21 plus or minus 3 seconds). A presumptive diagnosis of cholangitis was made, and the patient was given 30,000 units of penicillin every three hours. The high fever subsided, but there followed daily elevations of the temperature to as high as 100 to 101 F. A tentative diagnosis of carcinoma of the ampulla of Vater was made.

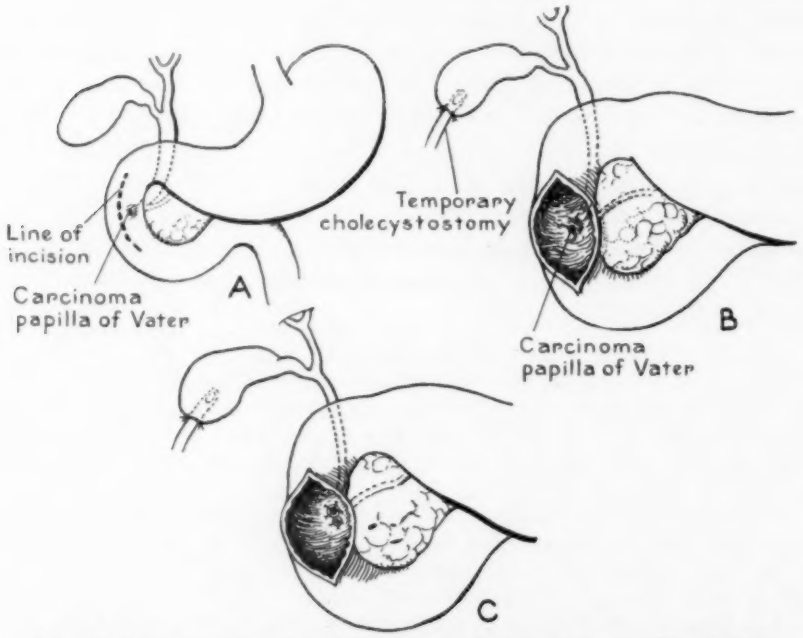

Fig. 10 (case 5).—Local excision for carcinoma of the papilla of Vater. *A*, line of incision for duodenotomy; *B*, small carcinoma of the papilla of Vater; *C*, local excision, with reimplantation of ducts and cholecystostomy.

On April 29 the abdomen was explored through a transverse incision in the upper abdominal area, continuous spinal anesthesia being used. The liver was dark green, swollen and nodular, wih nutmeg stippling. The gallbladder was approximately eight times the normal size and was thick walled. There was no obstruction palpable in the cystic or common ducts. There were no masses found in the head, body or tail of the pancreas. Palpation through the duodenum revealed a hard, swollen and distended ampulla of Vater, measuring approximately 2 cm.

A disk-shaped block of tissue containing the papilla and the ampulla of Vater was excised. The common bile duct and the pancreatic duct were anastomosed to the mucosa of the duodenum (fig. 10). A rubber tube was inserted into the common duct and lightly tied in place, with one end pointing into the duodenum.

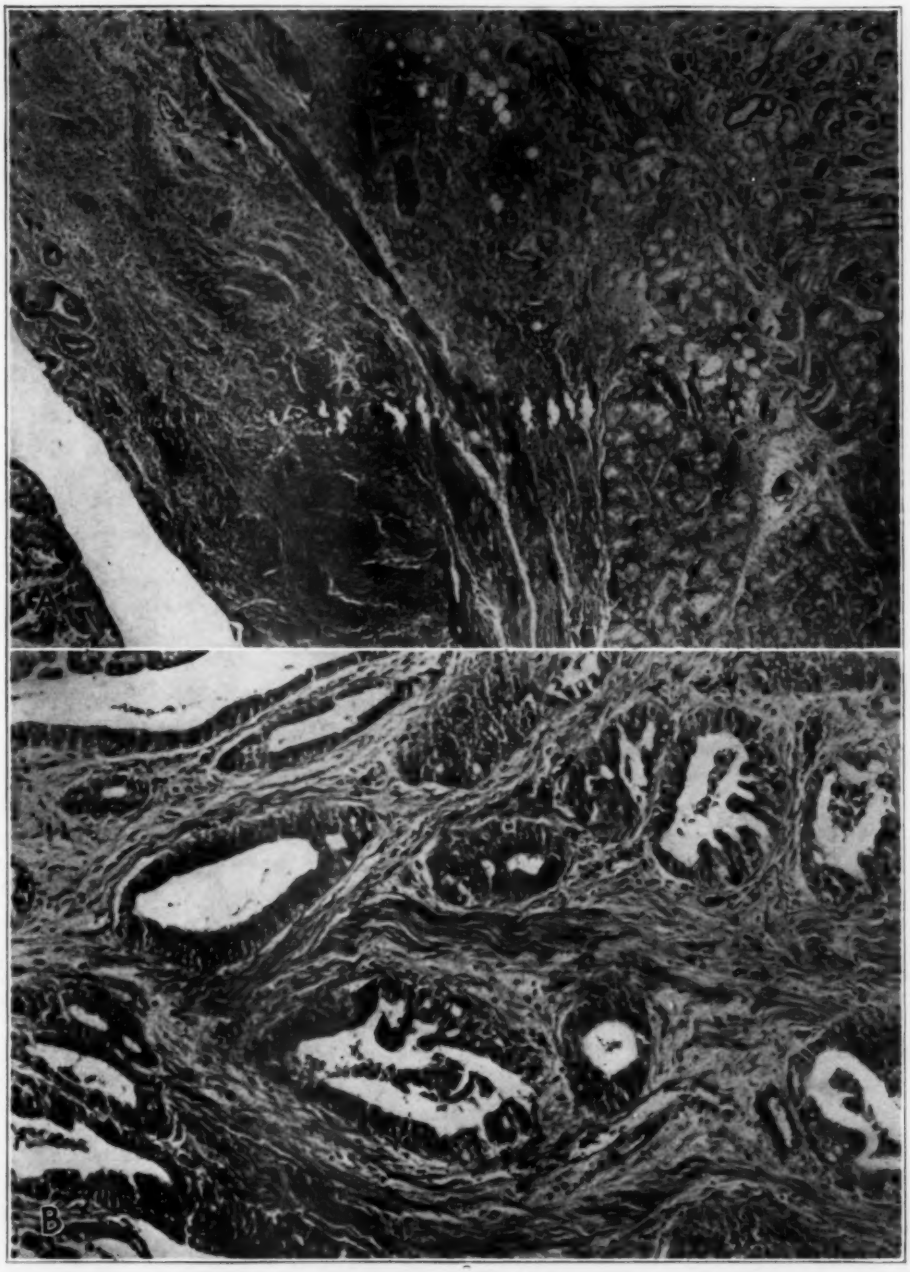

Fig. 11 (case 5).—*A*, photomicrograph through the ampulla showing infiltration of the carcinoma around the wall of the duct; *B*, photomicrograph showing adenocarcinoma of grade II histologic malignancy.

The duodenum was closed and external biliary drainage by means of cholecystostomy effected.

The pathologist's report was as follows: "The specimen consists of a disk-shaped piece of tissue measuring 1 by 1 by 0.5 cm. On one surface mucous membrane is evident, and in the center there is a small canal, evidently the opening of the bile duct into the duodenum. The ampulla feels firm, and the adjacent bile duct is dilated to several times the normal size. No definite tumor mass is noted on section. Microscopic examination shows an infiltration of the tissues by carcinoma cells which arrange themselves in irregular dark-staining glands. These penetrate for only a few millimeters into the subepithelial tissue (fig. 11). The diagnosis is adenocarcinoma of the ampulla of Vater, grade II."

On the first postoperative day there were complications in the form of severe generalized urticaria and pulmonary edema. This was followed by urinary retention due to prostatism. Tidal drainage was begun with an indwelling catheter to allay this last complication.

By May 3, the fourth postoperative day, the serum bilirubin was down to 16.5 mg. per hundred cubic centimeters, but there was a positive reaction for urobilinogen in a 1:160 dilution. The prothrombin time was normal. By the fifth postoperative day the blood urea nitrogen level had become elevated to 48.6 mg. per hundred cubic centimeters, but this gradually decreased to 31 mg. by the ninth postoperative day. During this time, the patient showed signs of "liver coma" and was extremely lethargic. His temperature ranged from 101 to 102 F. (by rectum). Culture of the urine showed Bacillus pyocyaneus and Bacillus coli and that of the biliary drainage B. coli, B. pyocyaneus and alpha streptococci.

His course during the next ten days was charcaterized by high fever with chills, which proved resistant to penicillin but did respond well to streptomycin. He was discharged with a Foley catheter in place on June 2, 1946, his thirty-third postoperative day.

His subsequent course was complicated by intermittent infections of the urinary tract, which were usually relieved by sulfadiazine therapy. Despite conservative measures, the infection of the bladder did not improve, and finally, on September 24 Dr. Gustavus Humphreys performed a cystotomy and vasectomy. His response to this was excellent, and two weeks later suprapubic prostatectomy was performed, with consequent relief and control of the urologic problem. At the time of his last examination, in May 1947, he was without complaints save that induced by aerophagia, a habit of long duration. A series of gastrointestinal roentgenograms was entirely normal except for a reflux of barium into the common duct for a distance of 4 cm. The serum bilirubin was 1.1 mg. per hundred cubic centimeters.

Comment.—The early manifestation of the lesion arising in the ampulla of Vater in this case indicated a good prognosis. A conservative procedure was deemed in order on the basis of the ascending cholangitis already present. It likewise was felt that the long-standing urinary retention on the basis of benign hypertrophy contraindicated a radical operation. Despite adequate internal and external bilary drainage, the cholangitis was a most obstinate postoperative problem. The dramatic response to streptomycin was shown on two occasions. Had the postoperative care not been successful and the diagnosis of complications bacteriologically proved, this would have been classified as another in-

stance of "liver death." Whether the liver or the urinary tract was most responsible is problematic, but the gradual enlargement of the liver would seem to indicate that the problem of ascending cholangitis was the predominant one. It is our belief that the operation performed in this case is to be used only for the patient whose general condition will not permit dissection en bloc. Aside from the objection to local excision in the surgical treatment of cancer, the danger of infection in the reestablishment of the biliary-intestinal anastomosis in the line of passage of gastrointestinal contents when the sphincteric protection of the ampulla is sacrificed is as likely as in the earlier types of radical pancreaticoduodenal resections. Complemental choledochoduodenostomy, as has been described by Baumgartner[42] in transduodenal resection for carcinoma of the ampulla, would seem a reasonable procedure in these cases insofar as a good mucosa to mucosa anastomosis can be established which will be less likely to undergo stenosis than will the reimplantation of the terminal portion of the duct, which lies in the scarred bed of the resection.

SUMMARY AND CONCLUSIONS

1. The scope of pancreaticoduodenal resection is defined.

2. Five cases of resectable neoplastic biliary obstructive lesions are presented. Four radical pancreaticoduodenectomies and one local excision were performed, without any operative deaths.

3. The detailed case histories recapitulate the development of the radical operation over the last ten years.

4. One patient survived for three years after operation, and another, whose cancer was still resectable two and one-half years after the onset of symptoms, is still living after four years, which indicates that much can be expected from the operation. One death three and one-half months postoperatively was the result of a biliary and pancreatic fistula. One patient is alive and shows no evidence of disease one year postoperatively, and 1 had recurrence of his disease nine months postoperatively.

5. The frequent complication of pancreatic fistula is a compelling surgical indication for pancreaticojejunostomy.

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42. Baumgartner, C. J.: Transduodenal Resection of Carcinoma of the Ampulla of Vater, West. J. Surg. **50**:250-253, 1942.

EFFECT OF EXCLUSIVE PARENTERAL FEEDING ON THE CLOSURE OF A PANCREATIC FISTULA

Study Made After Duodenopancreatic Resection for Carcinoma of the Ampulla of Vater

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THIS REPORT describes observations made on a patient with a complete pancreatic fistula. It is the first time, we believe, that the influence of exclusive parenteral feeding in such a case has been reported. Changes in pancreatic secretion were of special interest; of therapeutic importance was the spontaneous permanent closure of the fistula during the regimen.

REPORT OF A CASE

M. B., a 67 year old white man, entered the St. Louis City Hospital in May, 1947, with a history of jaundice of three weeks' duration. He had lost 50 pounds 22.7 Kg. of weight over a period of six months and had had a profound anorexia for this same period. His urine was dark, and he had light-colored stools. He had no pain whatever. He had had no chills or fever. The past history and the family history were noncontributory.

Physical exxamination revealed a poorly nourished white man appearing chronically ill. His skin was markedly icteric. Examination of the abdomen revealed no masses, tenderness or ascites. The liver was palpable 3 inches (7.6 cm.) below the costal margin on the right side. Rectal exxamination revealed no abnormality.

Laboratory data showed bile in the urine (4 plus) and no urobilinogen. The red and white blood cell counts were within normal limits except that slight anemia was revealed. The prothrombin time was 75 per cent of normal. The stools were acholic. The alkaline phosphatase content was 18.9 Bodansky units. The reaction to the cephalin-cholesterol flocculation test was negative. The icterus index was 90 to 120. The blood diastase level measured 460 mg. per hundred cubic centimeters, or about four times the normal level.

Proctoscopic examination revealed nothing abnormal. A punch biopsy of the liver revealed biliary cirrhosis. A series of gastrointestinal roentgenograms was made. The duodenum was reported to be rather large and atonic, with some de-

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From the Department of Surgery, Washington University Medical School and Barnes Hospital.

formity in the first portion. However, it contracted well with each peristaltic wave. It was felt that the deformity was due to an old healed duodenal ulcer. Examination of the colon showed considerable retention of the barium and evidence of a filling defect in the lower part of the sigmoid colon. A barium enema revealed complete obstruction at the rectosigmoid junction.

Because of these findings it was felt that the patient had a carcinoma of the sigmoid colon, with hepatic metastasis, producing biliary obstruction. However, at the time of operation (June 14, 1947) the sigmoid colon was found to be free of disease. The gallbladder was greatly dilated; palpation of the mobilized duodenum revealed a mass in the region of the ampulla of Vater, which was judged to be carcinoma. Accordingly, a radical pancreaticoduodenectomy was performed, followed by a choledochojejunostomy and gastrojejunostomy. The pancreatic duct was isolated and ligated with a fine silk ligature. The transected portion of the pancreas was closed with interrupted mattress sutures of medium silk. The abdomen was closed with stainless steel wire without drains.

Pathologic Report.—The specimen showed a papillary growth in the periampullary region which measured 8 by 6 by 1 cm. There was no ulceration. There was a definite stenosis, with dilatation of the pancreatic and common bile ducts. Microscopically the tumor proved to be a carcinoma of the ampulla of Vater which had not invaded beyond the muscularis mucosa. The lymph nodes were found to be free of carcinoma cells.

The immediate postoperative course was uneventful. On the seventh day the wound was red and indurated. Two days later there was definite evidence of a pancreatic fistula. The amount of pancreatic secretion reached 750 cc. per day. On July 29, 1947, the fistula closed at the skin edge, with the result that the temperature rose to 39 C. (102.2F.) and the blood diastase level rose to 1,590 mg. per hundred cubic centimeters. The wound reopened, with free drainage of pancreatic juice and subsidence of symptoms. During the following month, or eight weeks after the operation, the fistula persisted and showed no evidence of closure. The case was discussed with Dr. Robert Elman, who suggested a trial of complete gastrointestinal rest with parenteral feeding, for which the patient was transferred to the Barnes Hospital.

Procedure and Methods of Study.—The plan of therapy was presented to the patient as an experimental procedure. He readily assented because of his great desire to do anything which had any promise of hastening the closing of the fistula. It was possible to measure the rate of flow of the pancreatic juice with some accuracy because all the secretions were readily collected by a catheter which tightly filled the fistula opening. The number of drops per minute were counted for periods of from two to five minutes at fifteen minute intervals. Total twenty-four hour collections were also made.

As a normal control period, the rate of secretion and the composition of the pancreatic juice were studied for four days while the patient took a regular diet. During this time the patient ingested with his food all the pancreatic juice which escaped save that which was used for chemical analyses.

After this initial four day control period, he was given absolutely nothing by mouth, and parenteral alimentation via the intravenous route was carried out. This consisted of 2 liters of solution a day. The solutions contained 100 Gm. of dextrose per liter for a period of five days, 50 Gm. each of a mixture of crystalline amino acids[1] and dextrose for a period of four days and 50 Gm. each of hydro-

1. Supplied by Merck and Company, Rahway, N. J.

lyzed protein ("amigen"[2]) and dextrose for a period of seven days. In this way the gastrointestinal tract was given complete rest for a total period of sixteen days. Total collections of both urine and pancreatic juice were made and measured. These represented the total fluid loss, except for the insensible loss, as the patient had no stools during this period. The twenty-four hour output of water, sodium, potassium, chlorine, phosphorus and total nitrogen was measured in both the urine and the pancreatic juice. It was possible to do balance studies for each of these elements as the intake was constant for each period and was accurately known. The twenty-four hour excretion of creatinine was measured in the urine also. Blood samples were drawn every four or five days in order to determine the carbon dioxide--combining power and the chloride and serum amylase contents.

Methods Used: Sodium and potassium concentrations were determined with the flame photometer[3]; a 1 to 20 dilution of the pancreatic juice was made and

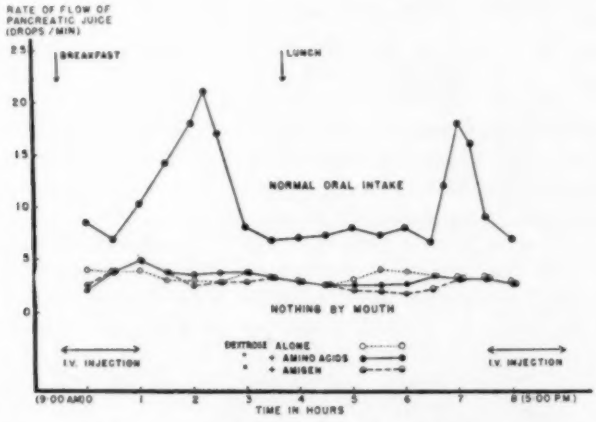

Fig. 1.—The rate of flow of pancreatic juice in response to a normal oral intake (upper curve) as compared with three forms of exclusive parenteral feeding (three lower curves). Note the stimulating effect of oral feeding in contrast to no stimulus during intravenous injections. Note also the low basal level of pancreatic secretion during parenteral feeding.

the average of five readings taken as the true value. The maximum deviation of scale readings considered acceptable was 2, which represents a deviation of one part per million at the aforementioned dilution. The chloride contents were determined by the Volhard-Harvey titration method[4] using silver chloride and back titration with a thiocyanate solution. Inorganic phosphorus was determined by the method of Fiske and Subbarow,[5] the transmission of light through the blue color which is developed being measured in the Coleman Universal spectrophotometer. Total nitrogen was measured by a macro-Kjeldahl method, and creatinine was estimated by the Folin method,[6] the Coleman spectrophotometer again being used. The *p*H was measured with the Beckman glass electrode *p*H meter. Serum amylase

2. Manufactured by Mead Johnson and Company, Evansville, Ind.
3. Supplied by the Perkin-Elmer Corporation, Glenbrook, Conn.
4. Harvey, S. C.: The Quantitative Determination of the Chlorides in the Urine, Arch. Int. Med. **6**:12 (July) 1910.
5. Fiske, C. H., and Subbarow, Y. J.: J. Biol. Chem. **66**:375, 1925.
6. Folin, O. J.: J. Biol. Chem. **17**:469, 1914.

was estimated by the somogyi method, the normal range being 80 to 150 units per hundred cubic centimeters.

Findings.—Rate of Flow of Pancreatic Juice and Twenty-Four Hour Output: While the patient was taking a regular diet, the volume of pancreatic juice per twenty-four hours was 580 to 625 cc. The basal rate of flow of pancreatic juice with the stomach empty was approximately 7.5 drops per minute. However, between three and three and one-half hours after the ingestion of a meal the rate of flow rose rather sharply to 18 to 20 drops per minute, and then it returned in about an hour to the basal rate (fig. 1). The increase in rate of flow would coincide rather well with the emptying of the stomach.

During the periods of exclusive parenteral alimentation, the twenty-four hour volume of pancreatic juice was found to be significantly smaller (fig. 2). During the days in which 10 per cent dextrose alone and 5 per cent dextrose plus 5 per cent crystalline amino acids were given, the twenty-four hour volume output was 235 to 300 cc., approximately half that secreted during the period on the oral

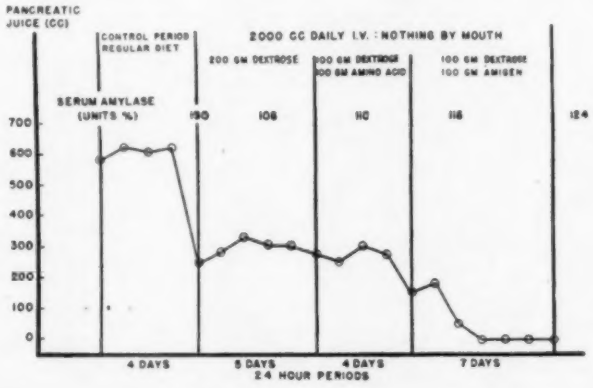

FIG. 2.—The twenty-four hour volume output of pancreatic juice during the control period of oral feeding and during the subsequent sixteen day period of exclusive parenteral feeding. Note the sharp reduction in the volume of pancreatic juice while the patient was on parenteral feeding. Secretion from the fistula ceased on the third day after the injection of "amigen" was begun.

diet. The rate of flow of the pancreatic juice was approximately 3.5 drops per minute, with no change in rate being noted during or after the intravenous injections. During the period when "amigen" was given the rate was slightly less, being about 3.0 drops per minute. The twenty-four hour output volume was also less, being 150 to 175 cc., but it decreased progressively so that during the third day after "amigen" was given the fistula closed completely and remained closed thereafter; alimentation was maintained for four more days, after which the patient took a regular diet by mouth (fig. 2).

The patient has now been followed for five months, during which there has been no drainage whatever. The total time from the start of the regimen exclusive of parenteral alimentation to the complete spontaneous closure of the fistula was twelve days.

Composition of the Pancreatic Juice: This is listed in table 1. The *p*H of the pancreatic juice was 8.0 to 8.5. This degree of alkalinity is due for the most part to the large amount of bicarbonate which was present. The twenty-four hour

output of sodium in the pancreatic juice was 108 to 115 milliequivalents during the period the patient was on the regular diet. The twenty-four hour output of potassium in milliequivalents was 2.0 to 4.0 while that of chlorine was 46.0 to 52.0 milliequivalents and that of phosphorus, measured as the divalent monohydrogen phosphate, was 0.56 to 0.60 milliequivalents. The discrepancy between these cations and anions is accounted for by the presence of bicarbonate.

When the patient was placed on strict parenteral alimentation the twenty-four hour output of sodium from the fistula dropped to 40.0 to 50.0 milliequivalents, the output of potassium dropped to 0.8 to 1.1 milliequivalents, that of chlorine to 22.0 to 25.0 milliequivalents and that of phosphorus to 0.15 to 0.38 milliequivalents. During the period "amigen" was given the amounts of the twenty-four

TABLE 1.—*Twenty-Four Hour Electrolyte Excretion in Pancreatic Juice*

Daily Intake	Sodium + (mEq)	Potassium + (mEq)	Chlorine − (mEq)	Phosphate =m (Eq)*
Regular diet	108.4	1.9	46.8	0.56
	115.2	2.0	51.8	0.60
	113.0	3.6	47.5	0.59
Nothing by mouth	36.8	0.7	21.9	0.15
(2,000 cc. by vein)	40.8	0.8	22.2	0.17
200 Gm. of dextrose	52.0	0.9	28.4	0.21
	50.8	1.1	23.4	0.29
	48.8	0.9	25.3	0.38
100 Gm. of dextrose	47.0	1.1	22.6	0.36
100 Gm. of amino acids†	40.4	0.8	21.2	0.24
	48.8	0.9	25.2	0.19
	44.8	0.9	25.6	0.16
100 Gm. of dextrose	21.9	0.4	14.9	0.24
100 Gm. of "amigen"‡	28.8	0.5	16.8	0.22

*Phosphate measured as the divalent monohydrogen phosphate.
†100 Gm. of amino acids contains 10.5 milliequivalents of sodium ion, 0.03 milliequivalents of potassium ion and 22.8 milliequivalents of chlorine ion.
‡100 Gm. of "amigen" contains 130 milliequivalents of sodium ion, 5.4 milliequivalents of potassium ion, 48.6 milliequivalents of chlorine ion and 13 milliequivalents of phosphate ion.

hour excretion were: sodium, 22.0 to 29.0 milliequivalents; potassium, 0.4 to 0.5 milliequivalents; chlorine, 15.0 to 17.0 milliequivalents, and phosphorus, 0.22 to 0.24 milliequivalents. However, these differences can largely be explained by the difference in volume, the concentrations varying definitely but the difference being small. For example, during the period of regular diet the concentration of sodium was 2.1 Gm. or 91.0 milliequivalents, per liter. This fell to 1.9 Gm., or 83.0 milliequivalents, per liter during the period of parenteral feeding.

Composition of the Urine: The sodium and chlorine output within a day or two of the onset of the parenteral injections fell to minute amounts, around 10 milliequivalents in twenty-four hours, undoubtedly because of the absence of any salt intake. This illustrates the ability of the body to conserve these elements. However, the continued loss of salt in the pancreatic juice soon led to hypochloremia.

The potassium and phosphorus contents of the urine were and continued to be somewhat higher and of proportionate amounts, i.e., 16 to 18 milliequivalents per twenty-four hours.

Nitrogen Balance: During the period the patient was on the regular diet the twenty-four hour output of nitrogen in the pancreatic juice was 0.38 to 0.50 Gm. This fell to 0.13 to 0.25 Gm. per twenty-four hours during the period of parenteral feeding. Again this is accounted for largely by the change of volumes inasmuch as the concentration was unchanged, i.e., 0.74 Gm. per liter with the regular diet as compared with 0.69 Gm. per liter with the parenteral regimen. Total nitrogen balances are shown in table 2. During the period the patient was given 10 per cent dextrose alone, there was negative nitrogen balance to the extent of 2.94 to 5.42 Gm. per day. During the periods he was given amino acids and "amigen," however, slight positive balance was maintained.

TABLE 2.—*Nitrogen Balance**

24 Hour Period	Intake	Output		Balance	Creatinine
		Urine	Pancreatic Juice		
1	0.00	5.27	0.15	—5.42	0.78
2	0.00	3.83	0.13	—3.96	0.66
3	0.00	2.78	0.20	—2.98	0.42
4	0.00	4.15	0.17	—4.32	0.81
5	0.00	2.75	0.19	—2.94	0.61
6	12.90	10.55	0.18	+2.17	0.60
7	12.90	13.05	0.25	—0.40	0.63
8	12.90	12.98	0.19	—0.27	0.67
9	12.90	12.35	0.16	+0.39	0.74
10	12.00	9.29	0.20	+2.51	0.57
11	12.00	7.69	0.16	+4.15	0.58
12	12.00	11.95	0	+0.05	0.49
13	12.00	10.89	0	+1.11	0.95
14	12.00	13.16	0	—1.16	0.96
15	12.00	10.02	0	+1.98	0.15
16	6.00+	5.96	0	+0.04	0.31

*All data are expressed as grams per twenty-four hours.

Blood Chemistry: At the start of this metabolic study, the serum amylase level was slightly elevated, i.e., 190 mg. per hundred cubic centimeters. During the period of parenteral feeding and immediately after closure of the fistula it remained near 120 mg., a normal value. The carbon dioxide-combining power remained normal throughout, ranging from 61.6 to 69.8 volumes per cent. The plasma chloride level was almost normal (98 milliequivalents) at the start, but it fell to 85 at the end of the period during which no chlorides were injected. This represents the loss of chlorides in the pancreatic juice. The patient, indeed, exhibited definite clinical evidence of dehydration, including a loss of several pounds in body weight. After the injection of "amigen," which contains about 1.5 Gm. of sodium and 0.9 Gm. of chloride per liter, this deficit was partly corrected and

the blood level rose to 91 milliequivalents. This is still somewhat low; it was restored to normal only when the patient's oral intake returned to normal. The deficit could have been avoided by the addition of sodium chloride to the fluids administered parenterally, particularly those containing only dextrose and crystalline amino acids.

Water Balance: The actual findings are presented in table 3. It will be seen that the total fluid intake was 2,000 cc. per day for sixteen days. To the volumes of urine and pancreatic juice was added 1,000 cc. for each day as the insensible loss. It can be seen that the water balance was on the negative side during the time the fistula drained and when the patient exhibited signs of dehydration due to salt deficiency. After the fistula closed, this was rapidly corrected, so that the over-all picture is one of good water balance, with an intake of 2,000 cc. daily.

TABLE 3.—*Water Balance**

24 Hour Period	Intake	Output		Balance	Accumulative Balance
		Urine	Pancreatic Juice		
1	2,000	1,100	235	—335	— 335
2	2,000	750	270	— 20	— 355
3	2,000	660	330	+ 10	— 345
4	2,000	1,250	300	—550	— 895
5	2,000	1,200	300	—500	—1,395
6	2,000	620	280	+100	—1,295
7	2,000	700	250	+ 50	—1,245
8	2,000	1,050	300	—350	—1,595
9	2,000	1,050	280	—330	—1,925
10	2,000	650	150	+200	—1,725
11	2,000	500	175	+325	—1,400
12	2,000	800	50	+150	—1,250
13	2,000	750	0	+250	—1,000
14	2,000	800	0	+200	— 800
15	2,000	700	0	+300	— 500
16	2,000	500	0	+500	0

*All figures are in cubic centimeters per twenty-four hours. One thousand cubic centimeters has been added to the daily output as an estimate of the insensible loss.

COMMENT

It would appear from this experiment that a regimen of complete gastrointestinal rest and parenteral alimentation is useful in accelerating the closure of a pancreatic fistula. It is realized that a pancreatic fistula does tend to close spontaneously even if nothing is done. However, the fact that the closure occurred within twelve days after the onset of therapy in this case would indicate that spontaneous closure was abetted thereby. This is further emphasized by the fact that the fistula drained copiously without sign of closure for eight weeks before complete gastro-

intestinal rest was started. The immediate and persistent fall by one half or more in the twenty-four hour output of pancreatic juice after the start of the experimental period probably indicates that the pancreas, free of normal food stimulation, secreted only at its basal rate. The drop in the serum amylase content from 190 to 120 units per hundred cubic centimeters may also be explained by the decreased stimulation of pancreatic secretion. This is also shown by the slight decrease in electrolyte and nitrogen concentrations. The more rapid decrease in secretion and the final closure of the fistula following the use of a protein hydrolysate instead of the solution of pure amino acids suggest that the former has a greater inhibiting effect. Similar inhibition of gastric secretion by hydrolyzed protein injected intravenously was observed by Crider and Walker[7]. Regardless of these differences, however, it would seem logical to assume that the lowered rate of pancreatic secretion was of value in hastening closure of the fistula.

The present experiment again shows that adequate nutrition can be maintained for a considerable period with the gastrointestinal tract at complete rest. The importance of the use of an amino acid mixture again demonstrated by the positive nitrogen balance which was observed in contrast to a loss of up to 5.00 Gm. of nitrogen per day during the period in which dextrose alone was given. Thus without these nitrogenous solutions any plan of gastrointestinal rest involves wastage of protein tissue. The solutions of crystalline amino acids and of hydrolyzed protein seemed equally effective in maintaining nitrogen balance.

The fact that the parenteral experiment ended with the patient in a state of exact water balance (table 3) suggests that a daily intake of 2 liters of fluid was adequate for this purpose at least for a period of sixteen days. The regimen, however, was deficient in salt, as shown by the transient dehydration which developed after a total absence of electrolyte intake. Undoubtedly, this would have occurred if sodium chloride had been added to the fluids containing dextrose alone or dextrose and crystalline amino acids.

The fact that the serum amylase level did not rise after cessation of external drainage suggested at first that the fistula had merely found another track which communicated with the intestine. However, strong evidence to the contrary is presented by the change in the character of the stools. During the preliminary period while the patient drank all his pancreatic juice (mixed with tomato juice) along with the regular diet, the stools were normal. During the period of parenteral feeding he had no stools. As soon as he took a regular diet after closure of the fistula the stools promptly became large, foul and fatty. If a communication with the intestine had become established, one would have expected the

7. Crider, R. J., and Walker, S. M.: To be published.

stools to have remained normal. It is felt that the acinar tissue became atrophic and that secretion actually ceased. Eventually, after several weeks the stools gradually assumed a more normal appearance. This may have been due to a late recommunication of the pancreas with the intestine or to a compensatory secretion of enteric glands.

SUMMARY

1. A study was made of the effect of an exclusive parenteral intake for sixteen days on a male patient in whom a pancreatic fistula developed after a one stage pancreaticoduodenectomy for carcinoma of the ampulla of Vater. The study includes data on sodium, potassium, chloride, phosphate, nitrogen and water balances. The parenteral fluids were limited to 2 liters per day which contained in successive periods dextrose alone, dextrose plus crystalline amino acids, and dextrose plus dydrolyzed protein.

2. Pancreatic secretion was greatly suppressed after the onset of complete gastrointestinal rest. On the twelfth day the fistula closed spontaneously and permanently. The greatest inhibition was shown by the solution of hydrolyzed protein.

3. It is inferred that the rapid closure was aided by the removal of pancreatic stimulation normally produced by food taken orally as well as by an actual inhibition of pancreatic secretion by intravenous injection of hydrolyzed protein.

PHOSPHATASE ACTIVITY IN BLOOD SERUM, BONE AND SOFT TISSUES FOLLOWING FRACTURE IN THE CAT

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AT THE TIME of fracture, the trauma which interrupts the continuity of a bone also ruptures the walls of numerous blood vessels in the periosteum, haversian canals and marrow. There results a more or less extensive hemorrhage at the site of fracture which, because of tissue juices from injured cells, clots rapidly. The fibrinous network of this clot is soon invaded by fibroblasts which come from the periosteum, endosteum, vessels, fasciae, stroma of muscle tissue and areolar tissue and the haversian canals. The hematopoietic cells of the marrow quickly disappear and are replaced by undifferentiated connective tissue, this change being much more rapid in the red marrow of young bones than in fatty marrow. Young blood vessels invade the clot as granulation tissue, these vascular buds consisting of capillaries surrounded by a thin layer of accompanying fibroblasts.[1] In the gap intervening between the bone ends the vessels are at right angles to the long axis of the bone.[2] Disposition of the fibrin fibrils in the clot is haphazard, for the most part, from one bone fragment to the other, the preosseous framework extending in every direction without any orderly arrangement. The invading connective tissue fibers follow the direction of the vascular buds and appear to take on a definite lobulated arrangement. According to the violence of the trauma, the periosteum is stripped up, and the preceding phenomena occur at a

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1. Bancroft, F. W.: (*a*) The Process of Bone Repair Following Trauma, Am. J. M. Sc. **147**:809-829, 1914; (*b*) The Use of Small Bone Transplants in Bridging a Bone Defect, Ann. Surg. **67**:457-459, 1918; (*c*) Bone Repair Following Injury and Infection, Arch. Surg. **5**:646-677 (Nov.) 1922; (*d*) Clinical deductions Following a Study of Bone Repair, New York State J. Med. **24**:827-831, 1924.

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greater or less distance from the point of fracture. All these events are accompanied with a marked regional hyperemia which has two extremely important effects: first, it causes congestion and edema of the periosteum and the cellular elements of the bone and hence a stasis of tissue fluids; secondly, by influencing the carbonic acid content of the blood and of the interstitial fluid toward an ionic acidity of the local medium it causes rarefaction of the bone ends, giving rise to the "local calcific surcharge" of Leriche and Policard.[3] These authors have emphasized that many factors enter into the process of bone resorption. There are blood factors having to do with the hydrogen ion content of the blood[4], circulatory factors concerned with the activity of the local interchange[5], connective tissue factors[6], depending on the maturity of the connective tissue, and possibly certain endocrine factors, more especially from the thyroid and gonads, and, lastly, mechanical factors dealing with pressure, traction, tangential movements and shearing stress, all working through the medium of the capillary framework of the connective tissue[7]. In the midst of this

3. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone, translated by S. Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

4. (*a*) Ravdin, I. S., and Jonas, L.: Studies of Calcium and Phosphorus Metabolism in the Fracture of Bones, Ann. Surg. **84**:37-41, 1926. (*b*) Ravdin, I. S., and Morrison, M. E.: Ossification After Fracture, Arch. Surg. **17**:813-828 (Nov.) 1928. (*c*) Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90-95, 1930. (*d*) Robison, R.: The Possible Significance of Hexosephosphoric Esters in Ossification, Biochem. J. **17**:286-293, 1917.

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6. Bodansky, O.: The Accelerant Effect of Alpha-Amino Acids on the Activity of Bone Phosphatase, J. Biol. Chem. **114**:273-288, 1936; The Effect of Alpha-Amino Acids and Magnesium on the Activity of Kidney and Intestinal Phosphatases, ibid. **115**:101-110, 1936; Are the Phosphatases of Bone, Kidney, Intestine and Serum Identical? ibid. **118**:341-362, 1937. Reis, J.: La nucleotidase et sa relation avec la desamination des nucleotides dans le coeur et dans le muscle, Bull. Soc. chim. biol. **16**:385-399, 1934. White, J. R.: Chronic Traumatic Osteomyelitis, New York, Paul B. Hoeber, 1919.

7. McEwen, W.: The Growth of Bone, Glasgow, James Maclehose & Sons, 1912. Murray, C. R.: Delayed and Non-Union in Fractures in the Adult, Ann. Surg. **93**:961-967, 1931; Healing of Fractures, Arch. Surg. **29**:446-464 (Sept.) 1934. Pagel, W., and Simmonds, F. H.: The Healing of Cavities, Am. J. M. Sc.

stasis the connective tissue fibers enlarge and multiply by processes which are histologic but poorly understood and are contained within homogeneous, highly refractile substance, the preosseous substance, assuming the shape of the bone trabeculae. When the process has reached this stage, the local calcium and phosphorus gradually precipitate in the preosseous, loosely meshed substance in the avascular zones between the blood vessels, forming a lacelike structure of new bone.[8] The *p*H of tissue fluid tends to be alkaline when this precipitation occurs, affording a favorable condition for the deposition of calcium salts in the callus tissue by increasing the rate of phosphatase activity and concurrently reducing the solubility of the calcium salts. Swenson[9] expressed the belief that the *p*H changes may influence the calcium ion concentration in the fracture hematoma, but there are probably more decisive changes in the phosphate ion concentration which make possible a precipitation of some form of calcium phosphate. Ely[10] has shown that the trabeculae of young bone begin first in the angle between the periostum and the cortex and from there grow into the organized clot, proceeding from the periphery to the center in a centripetal direction. Blaisdell and Cowan[11] found that the manner of branching and the position of the blood vessels determine the form, position and manner of continuity of the early osteoid trabeculae, which appear to be invariably laid down at a given distance from the blood vessels, the distance being in direct ratio to the size of the vessels. This process determines the form and branching of the haversian canals, the final arrangement of bone trabeculae being dependent on functional stress. Koch[12] demonstrated that the thickness and closeness of spacing of trabeculae in bone vary directly with the intensity of the stresses transmitted by them. Having met and completely traversed the clot, the trabeculae become thicker, and more mature bone is gradually formed, the

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197:281-286, 1939. Robison, R., and Soames, K. M.: The Possible Significance of Hexosephosphoric Esters in Ossification: II. The Phosphoric Esterase of Ossifying Cartilage, Biochem. J. **18**:740-754, 1924. Robison, R.; Macleod, M., and Rosenheim, A. H.: The Possible Significance of Hexosephosphoric Esters in Ossification: IX. Calcification in Vitro, ibid. **24**:1927-1941, 1930. Wolff, J.: Ueber die innere Architectur der Knochen und ihre Bedeutung für Frage vom Knochenwachsthum, Virchows Arch. f. path. Anat. **50**:389-450, 1870.

8. Albee, F. H., and Morrison, H. F.: Studies in Bone Growth, Ann. Surg. **71**:32-39, 1920.

9. Swenson, O.: Biochemical Changes in Fracture Hematoma, J. Bone & Joint Surg. **28**:288-293, 1946.

10. Ely, L. W.: Experimental Study of the Healing of Fractures, Arch. Surg. **5**:527-560 (Nov.) 1922.

11. Blaisdell, F. E., and Cowan, J. F.: Healing of Simple Fractures, Arch. Surg. **12**:619-654 (March) 1926.

12. Koch, J. C.: The Laws of Bone Architecture, Am. J. Anat. **21**:177-293, 1917.

final stages being the reestablishment of the marrow cavity and the communication of the haversian canals.

If disturbing variations occur in this complicated series of events, so in direct proportion does the chance of delayed union or of nonunion increase.[13] The larger the gap between the fragments, the greater the quantity of fibrous tissue which will require ossification; this enhances the possibility of fibrous union or pseudarthrosis in relation to the timing of ionization. Large spaces are filled with large clots, and in these the direction of fibrin fibrils, vascular buds, connective tissue fibers and haversian canals is apt to be transverse to the longitudinal axis of the bone, thus predisposing to pseudarthrosis formation. Large clots are also apt to degenerate and liquefy in their centers before they can be organized by the granulation tissue growing in from the periphery, thus forming cysts of serous fluid which are efficient barriers to bony union. Purely mechanical interposition of soft tissues, such as muscle, tendon or blood vessels or widely seperated fragments, of course precludes the possibility of primary bone union[14].

REVIEW OF STUDIES ON PHOSPHATASE ACTIVITY

The occurrence of phosphoric esters among the products of metabolism was recognized as early as 1850, when Gobley[15] demonstrated the presence of glycerophosphoric acid in a substance which he isolated from egg yolk and had named lecithin. In 1917 Robison,[4d] while working in the field of plant physiology with hexosemonophosphate, first considered that the phosphatase enzyme might be concerned with the deposition of calcium salts in bone. Robison and his associates[16] pointed out that in the mechanism of normal bone formation the intercellular fluids bathing the osteogenic cells contain salts of phosphoric esters, which are hydrolyzed by the phosphatase secreted by those cells. Thus the concentration of phosphate ions is increased locally at the site of a fracture to a point exceeding the solubility product of calcium phosphate and of the related compounds composing bone. In the presence of a higher hydrogen ion concentration there is deposition of bone salts from the locally supersaturated solution on the bone matrix. The activity of phosphatase frees the phosphate radical by splitting it from a hexosephosphoric ester and allowing it to unite with the calcium.

13. Ham, A. W.; Tisdall, F. F., and Drake, T. G. H.: Experimental Non-Calcification of Callus Simulating Non-Union, J. Bone & Joint Surg. **20**:345-352, 1938.

14. Gallie, W. E.: The History of a Bone Graft, Am. J. Orthop. Surg. **12**: 201-212, 1914.

15. Gobley: J. pharm. et chim. **17**:401, 1850; cited by Robison.[16]

16. Robison, R.: The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932.

Several investigators[17] have pointed out that the phosphatase present in the serum arises in large part in the bones, a fact based on the evidence of large concentrations of a phosphatase in the bones which appears to be identical with the phosphatase in the serum and with a phosphatase present in various animal tissues. Folley and Kay[18] have demonstrated phosphoric esters capable of hydrolysis in vitro by the bone enzyme in large amounts in erythrocytes and in relatively small amounts in blood plasma. Koichi Kamada[19] has shown that the appearance of phosphatase in the tissue of callus has a definite relation to the progress of healing of a fracture. Botterell and King[20] found that an increase in phosphatase content of bone and callus is observed in healing fractures in rabbits, accompanied with the formation of hypertrophic cartilage cells, osteoblastic activity and the formation of bone matrix but associated with no concomitant increase in serum phosphatase. The introduction of phosphatase into the site of experimental fractures does not appear to change the rate or quality of calcification of the bone matrix.[21] Wilkins and Regen[22] reported that the increase in phosphatase activity in fractured rabbit bone is more or less limited to the site of injury. Smith and Maizels[23] demon-

17. (a) Armstrong, A. R.; King, E. J., and Harris, R. I.: Phosphatase in Obstructive Jaundice, Canad. M. A. J. **31**:14-20, 1934. (*b*) Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: Serum Phosphatase in Disease of the Bone; Interpretation and Significance, Arch. Int. Med. **54**:88-110 (July) 1934. (*c*) Folley, S. J., and Kay, H. D.: The Phosphatases, Ergebn. d. Enzymforsch. **5**:159-212, 1936. (*d*) Jenner, H. D., and Kay, H. D.: Plasma Phosphatase: III. A Clinical Method for the Determination of Plasma Phosphatase, Brit. J. Exper. Path. **13**:22-27, 1932. (*e*) Kay, H. D., and Robison, R.: The Possible Significance of Hexosephosphoric Esters in Ossification: III. The Action of the Bone Enzyme on the Organic Phosphorus Compounds in Blood, Biochem. J. **18**:755-764, 1924. (*f*) Martland, M., and Robison, R.: The Preparation and Use of the Bone Phosphatase, ibid. **23**:237-242, 1929. (*g*) Mitchell, C. L., and Crawford, R. R.: Serum Phosphatase: Its Clinical Application in Diseases of the Bone, J. Bone & Joint Surg. **19**:630-639, 1937. (*h*) Neuberg, C., and Jacobsohn, K. P.: Fortgestzte Untersuchungem über den Wirkungsbereich der Phosphatase, Biochem. Ztschr. **199**:498-517, 1928.

18. Kay, H. D.: Kidney Phosphatase, Biochem. J. **20**:791-811, 1926; The Phosphatases of Mammalian Tissues, ibid. **22**:855-866, 1928; The Phosphatases of Mammalian Tissues: II Pyrophosphatase, ibid. **22**:1446-1448, 1928; Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249-266, 1930. Folley and Kay.[17e]

19. Kamada, K.: The Callus Phosphatase and Its Participation in the Healing of Fracture, Kukuoka acta med. **25**:207-267, 1932.

20. Botterell, E. H., and King, E. J.: Phosphatase in Fractures, Lancet **1**: 1267-1270, 1935

21. Hunsberger, A., Jr., and Ferguson, L. K.: Variations—Phosphatase and Inorganic Phosphorus in Serum During Fracture Repair, Arch. Surg. **24**:1052-1060 (June) 1932.

22. Wilkins, W. E., and Regen, E. M.: Course of Phosphatase Activity in Healing of Fractured Bone, Proc. Soc. Exper. Biol. & Med. **32**:1373-1376, 1935.

strated that the plasma phosphatase content is normal in case of fracture immediately after the injury but rises at the time the callus appears and falls to normal when the bone is completely healed. Peden[24] found an apparent increase in plasma phosphatase within the first few days after fracture in children, more especially when the fracture involved the femur.

Martland and Robison[25] have shown that phosphatase is not present in any cartilage prior to the appearance of a center of ossification and also that phosphatase is found wherever active ossification is taking place and is present in greater amounts in bone at the time when the deposition of calcium salts is highest. Fell and Robison[26] found that phosphatase fails to appear in nonossifying cartilage such as Meckel's cartilage, rib cartilage and tracheal cartilage. Various authors[27] have reported that the periosteum and the enlarged cartilage cells of the metaphysis of embryonic and infant bones are rich in phosphatase while the epiphysis beyond the zone of active ossification is comparatively deficient in the enzyme. Bodansky and Jaffe [17b] expressed the belief that the destruction of bone per se, unless accompanied with new bone or with osteoid formation, is probably not associated with a considerable rise of the serum phosphatase level. Kay[28] suggested that the slight amount of phosphatase activity which still persists in the bones of adults may be a part of a protective mechanism insuring throughout life a slight excess of the phosphate ions in the vicinity of the already deposited bone so that inorganic phosphate does not go again into solution.

Franseen and McLean[29] noted in all the tumor tissues examined from the osteoblastic types of osteogenic sarcoma that the phosphatase activity

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23. Smith, J., and Maizels, M.: The Plasma Phosphatase in Rickets and Scurvy, Arch. Dis. Childhood **7**:149-158, 1932.

24. Peden, O. D.: Plasma Phosphatase and Phosphorus During the Healing of Fractures in Children, Arch. Dis. Childhood **12**:87-90, 1937.

25. Martland, M., and Robison, R.: The Possible Significance of Hexosephosphoric Esters in Ossification: V. The Enzyme in the Early Stages of Bone Development, Biochem. J. **18**:1354-1357, 1924.

26. Fell, H. B., and Robison, R.: The Growth, Development and Phosphatase Activity of Embryonic Avian Femora and Limb-Buds Cultivated in Vitro, Biochem. J. **23**:767-784, 1929.

27. Fell, H. B., and Robison, R.: The Development and Phosphatase Activity in Vivo and in Vitro of the Mandibular Skeletal Tissue of the Embryonic Fowl, Biochem. J. **24**:1905-1921, 1930. King, E. J., and Hall, G. E.: The Phosphatase of Fetal Bone, Canad. M. A. J. **25**:44-46, 1931. Policard, A.; Pehn, M.; Roche, J., and Boucomont, J.: Repartition histologique de la phosphatase dans la zone d'ossification des os longs chez l'enfant normal et rachitique, Bull. d'histol. appliq. a la physiol. **8**:170-175, 1931. Martland and Robison.[25]

28. Kay, H. D.: The Function of a Phosphatase in Bone Formation, Brit. J. Exper. Path. **7**:177-180, 1926; Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384-422, 1932.

was high and that in those undergoing rapid osteogenesis an extraordinary degree of phosphatase activity was present. A high degree of phosphatase activity in both tumor tissue and blood plasma, therefore, seems to be peculiarly characteristic of the osteoblastic type of osteogenic sarcoma[30]. A rapid fall of the plasma phosphatase to a normal level after removal of the osteogenic focus was demonstrated by these investigators, who also found that the phosphatase activity becomes increased again with recurrence, which offers good evidence of the synthesis of the phosphatase enzyme by a neoplastic cell. Phosphatase activity may also be useful in a differential diagnosis between metastatic carcinoma of the bone, in which there is an increase in the plasma phosphatase, and multiple myeloma, in which condition the phosphatase in the blood is almost invariably normal[31].

Gutman and Gutman[32] found the serum phosphatase in patients with Paget's disease (osteitis deformans) to be relatively constant but increased above normal level. Wilkins, Regen and Carpenter[33] determined, in studying a patient with progressive myositis ossificans, that fibrous tissue and muscle taken from the region of the lesions in the preossification stage showed a high phosphatase activity, that of the fibrous tissue being greater than that of the adjacent muscle tissue. According to Morris and her associates,[34] an increase in plasma phosphatase is a valuable test of the rachitic state, in which the phosphatase is increased whenever the supply of calcium is unable to meet the demand of the bone cells as a result of defective intake of minerals or vitamin D.

THEORIES OF BONE REPAIR

The problem of the process of healing after fracture remains complex in all its details because of the multiplicity of the factors involved.

29. Franseen, C. C., and McLean, R.: The Phosphate Activity of Tissues and Plasma in Tumors of Bone, Am. J. Cancer **24**:299-317, 1935.

30. Woodard, H. Q.; Twombly, G. H., and Coley, B. L.: A Study of the Serum Phosphatase in Bone Disease, J. Clin. Investigation **15**:193-201, 1936.

31. Gutman, A. B.; Gutman, E. B., and Kasabach, H.: Serum Phosphatase Activity in Seventeen Cases of Osteoporosis Circumscripa of the Skull, Proc. Soc. Exper. Biol. & Med. **33**:295-297, 1935. Gutman, A. B.; Tyson, T. L., and Gutman, E. B.: Serum Calcium, Inorganic Phosphorus and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease of the Bones, Arch. Int. Med. **57**:379-413 (Feb.) 1936.

32. Gutman, A. B., and Gutman, E. B.: Paget's Disease: Relative Constancy of Serum Phosphatase Levels Over Periods up to Two Years, Proc. Soc. Exper. Biol. & Med. **33**:150-153, 1935.

33. Wilkins, W. E.; Regen, E. M., and Carpenter, G. K.: Phosphatase Studies on Biopsy Tissues in Progressive Myositis Ossificans: Report of a Case, Am. J. Dis. Child. **49**:1219-1221 (June) 1935.

34. Morris, N.; Stevenson, M. M.; Peden, O. D., and Small, J. M. D.: Significance of Plasma Phosphatase in Diagnosis and Prognosis of Rickets, Arch. Dis. Childhood **12**:1-70, 1937.

Ollier[35] in 1867 expressed the view that the periosteum is the chief agent in forming the callus, with the marrow taking a slight part and the bone itself taking the least share in the repair process. On the assumption that periosteum and endosteum are the sole organs for bone formation and repair, no explanation is available for the formation of extraskeletal bone. Kolodny[36] has asserted that after fracture the endosteum is unable to participate in callus formation until the intraosseal blood circulation recovers by formation of an anastomosis between the central portion of the nutrient artery and the metaphysial blood vessels through the peripheral portion of the torn branch of the nutrient artery. Ely[37] has pointed out that neither periosteum nor marrow is necessary for bone formation. In each tissue the conditions are appropriate for bone formation, with abundance of materials present; bone will be produced out of the fibrous tissue of the periosteum or out of the fibrous tissue in the marrow.

Other investigators believe that the so-called osteoblasts are the sole organs of bone repair after injury and that either these bone cells are liberated from their lacunae to reproduce and form new bone or wandering connective tissue cells, the fibroblasts, are drawn into the area of trauma and become osteoblasts.

On the other hand, Watt[38] and Peters[39] expressed the opinion that calcification occurs by means of a precipitation. If it is assumed that there is no definite bone-producing cell, the extracellular deposition of calcium salts has been explained by Bancroft[1e]. After injury, calcium salts in the proportions usually found in bone are deposited in the extracellular framework of connective tissue, and the connective tissue cell then becomes a bone cell by functional adaptation[40].

McKeown and his associates[41] enunciated the assumption that two phosphatase activities occur concurrently in the healing process following fracture. First a local response simultaneous with callus formation leads to calcification of the callus. Second, an overflow of phosphatase from

35. Ollier, L. X. E. L.: Traite experimental et clinique de la régeneration des os et de la production artificielle du tissue osseux, Paris, V. Masson & fils, 1867.

36. Kolodny, A.: The Periosteal Blood Supply and Healing of Fractures, J. Bone & Joint Surg. **5**:698-711, 1923.

37. Ely, L. W.: The Formation of Bone, Ann. Surg. **69**:225-229, 1919.

38. Watt, J. C.: The Deposition of Calcium Phosphate and Calcium Carbonate in Bone and in Areas of Calcification. Arch. Surg. **10**:983-990 (May) 1925.

39. Peters, J. P.: Chemistry and Physiology of Calcification, Am. J. Surg. **10**:530-539, 1930.

40. Huggins, C. B.: The Phosphatase Activity of Transplants of the Epithelium of the Urinary Bladder to the Abdominal Wall Producing Heterotopic Ossification, Biochem. J. **25**:728-732, 1931.

41. McKeown, R. M., and Ostergren, J. I.: The Phosphatase Content of Fractured Bone, Proc. Soc. Exper. Biol. & Med. **29**:54-56, 1931. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats, Arch. Surg. **24**:458-491 (March) 1932.

the site of fracture plus stimulation to increased formation of phosphatase occurring at all phosphatase centers in response to a substance elaborated at the site of the fracture leads to a generalized skeletal reaction resulting in greater skeletal strength from accelerated calcification.

PLAN OF PRESENT EXPERIMENTS

The purpose of this study has been to determine the local phosphatase activity in the bone and soft tissues at the site of a bone defect during the period of repair processes up to three months as compared with the phosphatase activity in the blood serum. Investigative work previously has

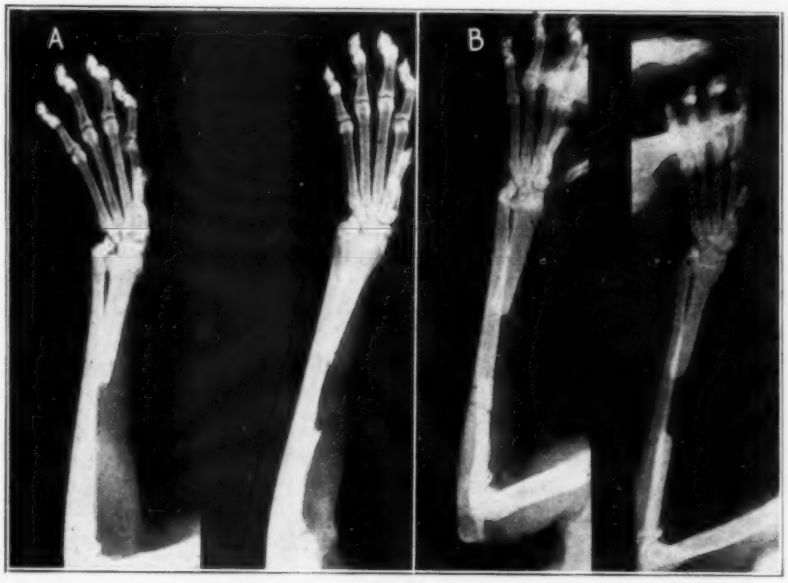

FIG. 1.—*A*, roentgen ray study of right forearms of cats 210 and 211 on Dec. 19, 1938, seven days after operation; *B*, roentgen ray study of right forearms of cats 211 and 210 on March 9, 1939, eighty-seven days after operation.

been carried out mostly on the subject of the healing of simple fractures. In this study it was desired to note the phenomena at the site of a bone defect in which union definitely could not occur in the bone itself.

Thirty cats weighing from 2.2 to 4.9 Kg. were used in this study. The age of these animals was not determined. The experimental work was done between December and March. The procedures carried out and the routine observed were as nearly identical as possible in each case and were not varied in any manner throughout the study in order to eliminate any untoward results in so far as possible. The animals were maintained on a routine diet consisting chiefly of meat, milk, bread and vegetables. They were kept indoors in cages not accessible to direct sunlight. Anesthesia was carried out by using a 35 mg. dose of pentobarbital sodium per

kilogram, given by the intraperitoneal route. Occasionally it was necessary to supplement this with a small amount of ether given in a cone. A dorsal incision was made near the medial border of the right forearm of each animal and the radius exposed at its middle third[42]. The periosteum was reflected from the radial shaft, and 2 cm. of bone was excised together with specimens from the surrounding soft parts. A tourniquet was applied above the elbow to reduce the bleeding. Two centimeters of bone was excised to assure a uniform loss of bony continuity, and there was no bridging of this gap between the ends of the bone fragments during the process of healing. The wound was closed with interrupted black silk sutures. No splint was necessary. A dry dressing was occasionally used when necessary to control oozing from the wound. The animals were killed and examined at intervals ranging from six hours to three months after the operation. The site of the bone defect in the radius was exposed, and 1 cm. of bone, including the callus, was excised from each radial fragment and specimens of the soft tissues filling and surrounding the bony defect obtained. At the time of each operation and each autopsy, 10 cc. of blood was obtained by cardiopuncture. The blood was allowed to clot, and at the end of one hour the specimen was centrifuged and the blood serum obtained. Roentgenographic studies were made prior to operation, again after operation at an interval of from seven to twelve days and finally at sixty and ninety days after operation. Callus formation may be faintly noted in the roentgenograms taken after the seventh day (fig. 1*A*). In the roentgenograms made on the sixtieth and ninetieth days the callus is more mature, rounding off the ends of each bony fragment but in no case bridging the gap between the fragments (fig. 1*B*) All the roentgenograms made were practically identical in appearance and detail with those shown here.

Phosphatase activity in the blood serum was determined on 1 cc. samples by Bodansky's method[43]. The samples of bone were stripped of all adventitious tissue and broken up into small particles. Aqueous extracts of bone and tissue were prepared by thorough grinding of each specimen with a glass pestle in a glass mortar with an equal volume by weight of so-called chemically pure sand, an equal volume by weight of distilled water being used. Each preparation was allowed to stand in the refrigerator for forty-eight hours, after which time the supernatant fluid extract was removed and 1 cc. samples were used for the determination of phosphatase activity by Bodansky's method. It is to be noted that at no time were these aqueous extracts filtered or centrifuged,

42. Horsburgh, D. B., and Heath, J. P.: Atlas of Cat Anatomy, Stanford University, Calif., Stanford University Press, 1938.

43. Bodansky, A.: Determination of Plasma Phosphatase, Proc. Soc. Exper. Biol. & Med. **28**:760-762, 1931; Determination of Serum Inorganic Phosphate and of Serum Phosphatase, Am. J. Clin. Path. (Tech. supp.) **7**:51-59, 1937.

since Franseen and McLean reported that filtration or centrifugation results in variable and occasionally considerable loss of phosphatase activity.

Inasmuch as erythrocytes contain large quantities of phosphoric esters, every effort was made to reduce hemolysis in specimens to a minimum. Although there was variation in the amount of hemolysis in each specimen, it was considered that this factor was operating constantly throughout the whole range of experiment, since a certain amount of hemorrhage occurred in each case on removal of specimens of either bone or tissue.

METHODS

Serum Phosphorus.—To 1 cc. of serum add 9 cc. of 5 per cent trichloracetic acid (Baker). Mix by a single inversion of the test tube and filter after fifteen minutes, using no. 40 Whatman ashless filter paper. To 5 cc. of the filtrate add 4 cc. of a 7.5 per cent sodium molybdate-sulfuric acid mixture (dissolve 45 Gm. of ammonia-free molybdic acid in 125 cc. of five times normal sodium hydroxide and dilute to 1,000 cc. with distilled water) and 1 cc. of stannous chloride solution (dissolve 15 Gm. of stannous chloride in 25 cc. of concentrated hydrochloric acid[44]). Calculation is done in the colorimeter, with the use of Beer's table,[45] the reading being multiplied by 200 to give the amount of inorganic phosphorus present in milligrams per hundred cubic centimeters. The proteins are precipitated by the trichloracetic acid. Adding the molybdic sulfuric acid mixture allows the formation of a phosphomolybdic salt. On the addition of the stannous chloride, the phosphomolybdic acid is reduced, forming colloidal oxide of molybdenum which may be compared in the colorimeter with a known standard solution. (Dissolve 0.4394 Gm. of potassium phosphate in a 1,000 cc. flask. Add 5 cubic centimeters of concentrated sulfuric acid and dilute to volume with distilled water. Four cubic centimeters of this solution to 100 cc. of distilled water is used for the known standard. Five cubic centimeters of this standard contains 0.02 mg. of phosphorus.)

Serum Phosphatase.—For ten minutes at 37 C., preheat 10 cc. of a substrate solution (500 mg. of sodium-beta-glycerophosphate and 0.424 Gm. of sodium diethylbarbiturate per hundred cubic centimeters of distilled water). Add 1 cc. of blood serum and mix by single inversion of the test tube. Place in incubator at 37C. for exactly one hour. At the end of the hour, the tube is placed in ice water. Then add 9 cc. of 10 per cent trichloracetic acid (Baker), mix and filter after fifteen minutes, using no. 40 Whatman ashless filter paper. Proceed with the determination as for blood serum phosphorus, using 5 cc. of the filtrate, 4 cc. of 7.5 per cent sodium molybdate-sulfuric acid mixture and 1 cc. of stannous chloride solution. Calculate in the colorimeter, using a known standard solution. The reading from Beer's table[45b] is multiplied by 400 and the amount of phosphorus

44. Kuttner, T., and Lichtenstein, L.: Micro-Colorimetric Studies: II. Estimation of Phosphorus; Molybdic Acid—Stannous Chloride Reagent, J. Biol. Chem. **86**:671-676, 1930.

45. Bodansky, A.; Hallman, L. F., and Bonoff, R.: (*a*) Deviation from the "Beer Law" in the Kuttner-Cohen Method for Determination of Phosphorus, Proc. Soc. Exper. Biol. & Med. **28**:762-763, 1931; (*b*) Phosphatase Studies: I Determination of Inorganic Phosphate; Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, J. Biol. Chem. **99**:197-206, 1932; (*c*) II. Determination of Serum Phosphatase: Factors Influencing the Accuracy of the Determination, ibid. **101**:93-104, 1933.

TABLE 1.—*Determinations of Phosphorus and Phosphatase*

Interval	Cat	Date of Operation	Phosphorus; Mg. per 100 Cc.			Phosphatase, Units per 100 Cc.		
			Serum	Bone	Tissue	Serum	Bone	Tissue
6 hr.	232	3/ 3/39	6.58	7.20	6.26	3.54	2.48	4.74
	232	3/ 3/39	6.70	4.46	6.32	3.22	4.42	4.64
	233	3/ 3/39	7.26	5.92	6.82	2.66	5.44	2.94
	233	3/ 3/39	5.60	4.74	5.32	5.12	3.30	2.08
12 hr.	234	3/10/39	3.58	3.16	4.34	2.78	3.60	0.90
	234	3/10/39	3.58	3.16	3.50	2.46	0.76	2.86
	235	3/10/39	1.98	3.02	3.16	4.14	3.22	2.84
	235	3/10/39	3.94	3.56	3.32	2.74	3.60	4.52
2 days	264	3/16/39	2.68	4.60	2.90	2.60	2.84	6.18
	264	3/18/39	5.68	4.28	5.44	2.40	4.32	1.24
	265	3/16/39	2.82	2.52	3.36	2.38	5.12	6.96
	265	3/18/39	5.32	4.84	6.36	0.68	2.08	1.16
3 days	266	3/16/39	2.88	3.70	5.28	3.60	9.70	4.96
	266	3/19/39	4.10	3.38	4.68	3.02	11.02	3.32
	268	3/21/39	2.88	3.20	4.06	2.24	3.20	3.06
	268	3/24/39	3.82	3.78	5.40	1.42	4.66	2.80
4 days	269	3/21/39	3.00	4.66	4.28	2.48	0.22	3.04
	269	3/25/39	4.62	7.20	4.54	1.06	2.36	3.50
	270	3/21/39	3.88	2.54	4.48	2.20	2.46	2.56
	270	3/25/39	3.96	4.92	5.60	2.20	5.32	3.00
5 days	271	3/21/39	3.24	3.00	5.08	1.16	2.20	1.64
	271	3/26/39	6.20	4.22	3.98	2.00	8.94	8.06
	272	3/21/39	5.12	4.08	5.12	1.20	4.28	3.48
	272	3/26/39	5.48	5.24	7.92	3.20	9.56	5.48
6 days	230	3/16/39	5.78	9.42	9.98	1.54	8.18	8.02
	230	2/22/39	5.82	3.52	3.48	0.00	1.68	0.60
	*231	2/16/39	7.46	5.78	11.20	3.02	4.78	4.36
	231	2/22/39	6.76	2.68	5.60	0.00	2.44	2.40
7 days	228	2/ 2/39	1.94	7.78	4.66	4.82	5.86	8.86
	228	2/ 9/39	8.62	6.82	5.60	9.50	14.70	15.92
	229	2/ 2/39	2.00	7.10	6.82	3.32	0.02	9.02
	229	2/ 9/39	9.64	8.08	10.50	5.04	12.12	9.70
12 days	226	1/23/39	6.06	6.16	9.42	0.14	0.76	0.00
	226	2/ 2/39	5.40	8.44	3.84	2.60	12.28	8.36
	227	1/23/39	6.26	5.44	8.26	2.14	0.16	0.00
	227	2/ 2/39	5.48	6.32	2.74	5:16	14.68	16.10
14 days	222	1/16/39	5.44	4.20	6.42	1.68	2.08	3.98
	222	1/30/39	5.92	3.98	3.44	1.72	11.42	8.68
	223	1/16/39	4.98	4.78	8.70	1.30	0.00	0.54
	223	1/30/39	5.16	6.20	3.64	2.12	10.84	9.08
30 days	224	1/23/39	4.78	4.68	5.12	1.78	2.20	3.76
	224	2/23/39	6.06	4.20	8.62	1.82	7.64	2.58
	225	1/23/39	5.12	8.08	6.02	1.12	0.48	0.00
	225	2/23/39	7.14	3.56	3.84	0.10	17.68	4.40
45 days	220	1/ 4/39	5.48	6.36	8.00	3.36	0.92	2.88
	220	2/ 9/39	4.56	8.90	8.16	7.00	10.38	5.36
	221	1/ 4/39	6.76	7.34	8.70	2.68	6.94	2.58
	221	2/ 9/39	8.26	7.26	9.52	5.02	12.22	10.96
60 days	216	1/ 9/39	3.56	7.38	6.32	1.08	1.14	3.61
	216	3/ 9/39	4.08	3.26	3.72	0.00	6.10	2.64
	219	12/28/38	5.78	3.60	8.26	0.58	2.72	0.42
	219	3/ 2/39	5.20	2.22	6.76	1.44	2.86	4.14

Interval	Cat	Date of Operation	Phosphorus; Mg. per 100 Cc.			Phosphatase, Units per 100 Cc.		
			Serum	Bone	Tissue	Serum	Bone	Tissue
75 days	213	12/19/38	6.20	5.08	7.70	0.40	1.20	0.60
	213	3/ 2/39	4.72	3.22	5.48	1.84	4.54	10.80
	214	12/19/38	7.76	5.20	5.48	0.00	1.14	0.56
	214	3/ 2/39	5.16	4.36	7.00	1.84	2.44	7.04
90 days	210	12/12/38	5.48	6.48	3.92	2.96	4.16	0.00
	210	3/ 9/39	4.62	4.72	4.92	1.26	3.04	2.64
	211	12/12/38	4.82	5.28	7.92	1.58	0.60	0.00
	211	3/ 9/39	5.12	4.14	5.40	1.92	4.74	1.92

subtracted, leaving the uits of phosphatase per hundred cubic centimeters. A unit of phosphatase activity is that amount which will liberate 1 mg. of phosphorus as the phosphate ion during the hour of incubation. The difference between the total inorganic phosphorus after incubation and the blood serum phosphorus, both expressed on the basis of 100 cc. of blood serum, equals the units of phosphatase activity per hundred cubic centimeters. One cubic centimeter samples of the aqueous bone and tissue extracts were used for the detrminations exactly the same as for the blood serum sample.

RESULTS OF EXPERIMENTS

Table 1 is a record of the determinations of phosphorus and phosphatase. There are two series of determinations for each animal, one series made at the time of operation and the second series after a varying interval of time. Two animals were used in order to allow a control for the determinations made at each time interval. The results agree favorably with the normal values obtained by Flood and his co-workers,[46] who found in the blood serum of 10 control cats a variation in inorganic phosphorus of from 3.9 to 5.5 mg. per hundred cubic centimeters and blood serum phosphatase values ranging from 1.1 to 4.0 Bodansky units per hundred cubic centimeters.

Figures 2 to 7 have been prepared to show the percentage change occurring in each animal with regard to both the phosphorus and the phosphatase activity at each time interval in which determinations were made. In order to produce a curve, the first cats operated on at each time interval (table 1) have been grouped together, and the percentage changes found in the determinations on this group are shown by a solid line. Similarly, the second cats operated on at each interval have been grouped together, and the percentage changes in this second group are represented by a dotted line. As an average result could not be based on only 2 animals, it was felt that this method of representation would best allow for examination of the general trend in the phenomena observed in the series of experiments.

46. Flood, C. A.; Gutman, E. B., and Gutman, A. B.: Serum and Urine Phosphatase Activity in the Cat After Ligation of the Common Bile Duct, Am. J. Physiol. **120**:696-702, 1937.

Interesting to note in each of the six charts is the fall in activity, common to all six factors studied, which occurred on the sixth day, at a time presumably consistent with the process of ionization and deposition of calcium salts at the site of the bone defect. The blood serum phosphorus content (fig. 2) shows a decided rise on the seventh day; otherwise fluctuation is comparatively mild throughout the period of study.

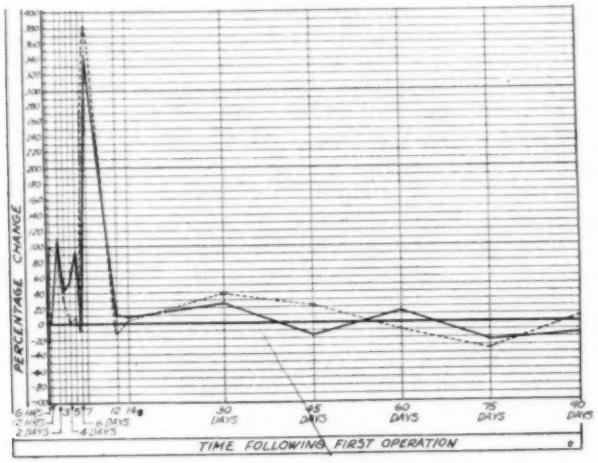

Fig. 2.—Percentage change in phosphorus activity in blood serum.

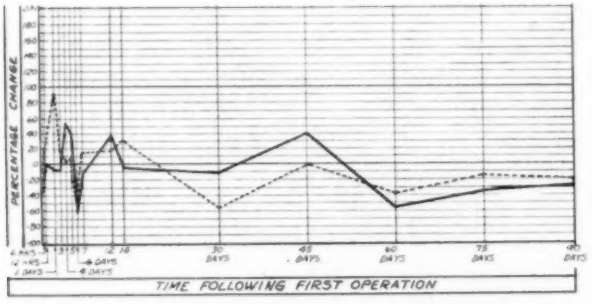

Fig. 3.—Percentage change in phosphorus activity in bone.

Figure 3 records only mild activity in the phosphorus content of bone, except for the previously mentioned drop on the sixth day. This would coincide with the findings of Murray,[47] who observed no notable changes in the blood phosphorus in patients treated in the fracture service at the Presbyterian Hospital in New York, where weekly studies of blood phosphorus and blood calcium were made for over a year on all patients being treated for fracture.

47. Murray, C. R.: The Repair of Fractures, Minnesota Med. **13**:137-152, 1930.

In figure 4 is noted a rise in phosphorus content in the tissue on the second day. Decreased activity is found on the sixth and on the twelfth to fourteenth days, which might be expected as a result of the local demand coincident with ionization and deposition of calcium salt.

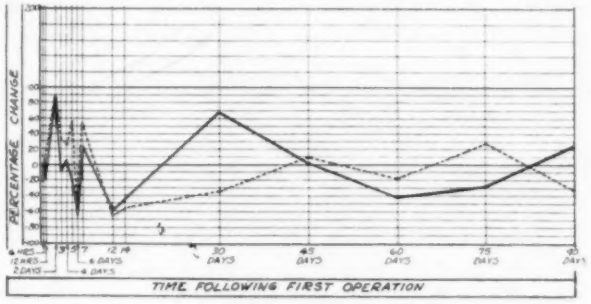

Fig. 4.—Percentage change in phosphorus activity in tissue.

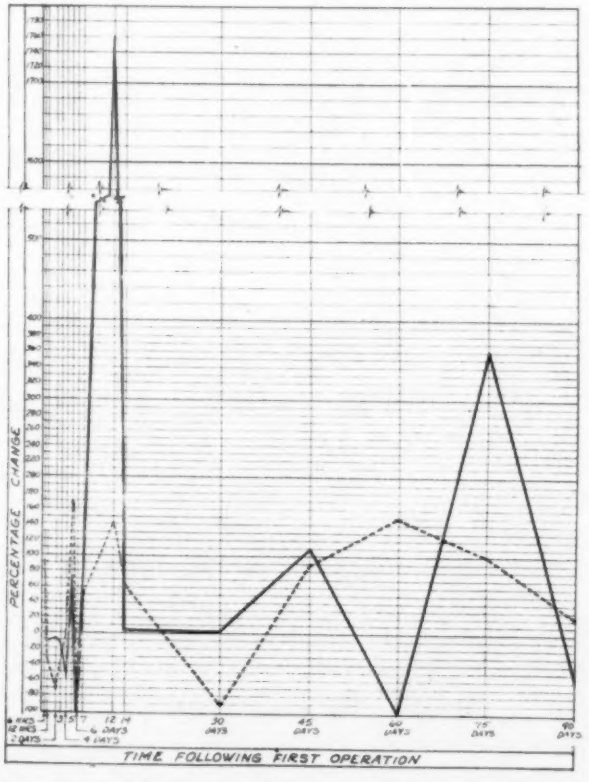

Fig. 5.—Percentage change in phosphatase activity in blood serum.

The phosphatase activity in the blood serum (fig. 5), after an increase on the fifth day, shows a decrease on the sixth day, followed by its

maximum rise on the twelfth day. Activity remains sustained through the seventy-fifth day of the study, with a decrease present between the fourteenth and forty-fifth days.

The bone phosphatase shows initial activity on the fourth and fifth days (fig. 6). This is followed by a decrease on the sixth day and then a recurrence of activity reaching its height on the twelfth day and being well sustained throughout the remaining periods of observation.

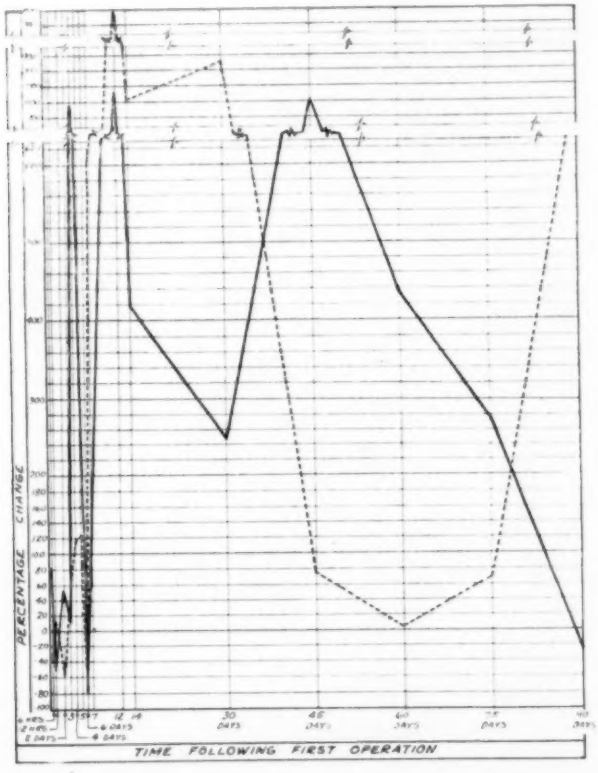

Fig. 6.—Percentage in phosphatase activity in bone.

The phosphatase activity in the tissues (fig. 7) is increased as early as the twelfth hour and then subsides, to recur on the fifth day. There is a decrease on the sixth day. The greatest activity is found on the fourteenth and seventy-fifth days. It is difficult to explain why there should be this period of high activity so late after production of the bone defect. It may represent an increment resulting from a relatively slow synthesis of the enzyme.

FURTHER STUDIES

Because of the phosphatase activity in blood serum, bone and tissue previously noted, it was decided to repeat the work which had been done up to this time and to carry out the determinations of phosphatase accord-

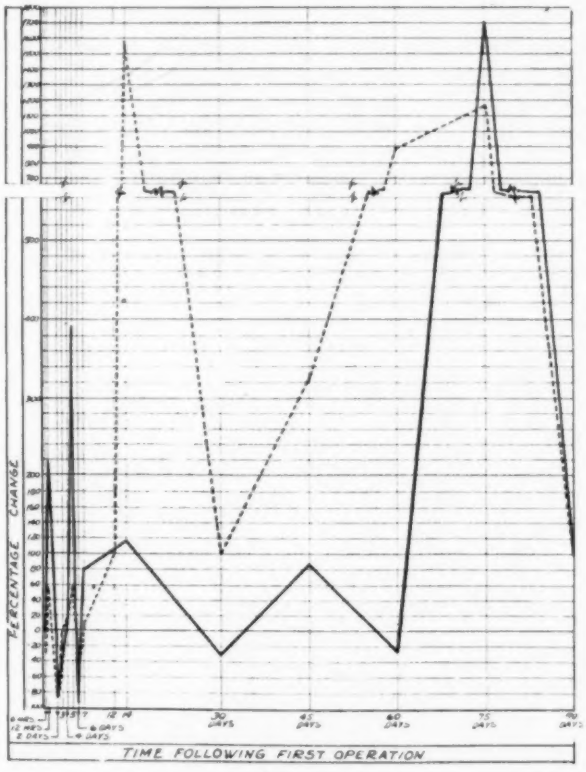

Fig. 7.—Percentage change in phosphatase activity in tissue.

ing to King and Armstrong's method. These further studies were considered necessary in order to further check the preceding results. The King and Armstrong method[48] was considered to be more accurate than the method used in the previous studies. This method depends on the

48. Huggins, C., and Hodges, C. V.: Studies on Prostatic Cancer: I. The Effect of Castration of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate, Cancer Research **1**:293-297, 1941. Huggins, C.; Stevens, R. E., Jr., and Hodges, C. V.: Studies on Prostatic Cancer: II. Effects of Castration on Advanced Carcinoma of the Prostate Gland, Arch. Surg. **43**:209-223 (Aug.) 1941. Huggins, C.; Scott, W. W., and Hodges, C. V.: Studies on Prostatic Cancer: III. The Effects of Fever, of Desoxycorticosterone and of Estrogen on Clinical Patients with Metastatic Carcinoma of the Prostate, J. Urol. **46**:997-1006, 1941.

ability of the enzyme to liberate phenol from disodium monophenylphosphate.

Accordingly, 14 cats were subjected to the same procedure outlined in the previous study.

Method.—Essential Solutions: The essential solutions are prepared as follows.

1. Buffer substrate at p_H 5 is prepared by dissolving 21 Gm. of citric acid in distilled water and adding 200 cc. of normal sodium hydroxide solution. Dissolve separately 1.09 Gm. of disodium monophenylphosphate and add to the foregoing. Dilute to 1 liter in a volumetric flask.

2. Diluted phenol reagent is prepared by adding 3 volumes of distilled water to 1 volume of the phenol reagent of Folin and Ciocalteau. The latter may be purchased, or it may be prepared as follows: Dissolve 100 Gm. of sodium tungstate and 25 Gm. of sodium molybdate in 700 cc. of water in a 1,500 cc. Florence flask. Add 50 cc. of syrupy (85 per cent) phosphoric acid and 100 cc. of concentrated hydrochloric acid. Connect the flask with a reflux condenser by means of a cork or rubber stopper wrapped in tinfoil. Boil the solution gently for ten hours. At the end of this time add 150 Gm. of lithium sulfate, 50 cc. of water and a few drops of liquid bromine. Cool, dilute to 1 liter and filter. The finished reagent should not have a greenish tint. It should be kept well protected from dust because organic materials will gradually produce slight reductions.

3. Stock standard phenol solution (containing about 100 mg. per hundred cubic centimeters) may be purchased, or it may be prepared by dissolving 1 Gm. of crystalline phenol in tenth-normal hydrochloric acid and making up to 1 liter with tenth-normal hydrochloric acid in a volumetric flash. The solution keeps indefinitely.

The exact phenol content can be determined by titration as follows: Transfer 25 cc. of the solution to a 250 cc. flask, add 50 cc. of tenth-normal sodium hydroxide and heat to 65 C. To the hot solution add 25 cc. of tenth-normal iodine solution; stopper the flask and let it stand at room temperature for thirty to forty minutes. Add 5 cc. of concentrated hydrochloric acid and titrate the excess of iodine with tenth-normal thiosulfate solution. The appropriate factor being used in each case, milligrams of phenol per hundred cubic centimeters of stock standard solution will equal 6.27 × (factor for iodine solution × 25 minus factor for thiosulfate solution × cc. used).

4. Diluted standard phenol solution should contain exactly 10 mg. per hundred cubic centimeters. Measure out from a burette into a 100 cc. volumetric flask the number of cubic centimeters equal to

$$\frac{1000}{\text{mg. of phenol per 100 cc. of stock standard solution (no. 3)}}$$

Dilute with distilled water to 100 cc. This solution keeps for at least three months in the refrigerator.

5. Phenol solution and reagent for colorimeter standard must be made up daily. Add 5 cc. of diluted standard phenol solution (no. 4) and 15 cc. of diluted phenol reagent (no. 2) to a 50 cc. volumetric flask and add distilled water to the mark.

Solutions for standardization: For the determination of the exact phenol content of the stock standard phenol solution, the following solutions and procedures are necessary:

Potassium iodide solution, 10 per cent. Dissolve 100 Gm. of potassium iodide in distilled water in a 1 liter volumetric flask and dilute to the mark. This solution keeps indifinitely in a dark bottle. It is used in making up the standard iodine solution and in standardizing the thiosulfate solution.

Standard iodine solution (approximately tenth-normal) for standardizing the stock standard phenol solution. Measure out about 300 cc. of the 10 per cent potassium iodide solution. Weigh out into a weighing bottle 13 Gm. of crystalline iodine and transfer to a 1 liter volumetric flask. Any crystals of iodine which cling to the walls of the weighing bottle are washed into the flask with the iodide solution. The remainder of the iodide solution is then poured into the flask, the contents are shaken until all the iodine has dissolved and the solution is diluted to volume with water. Standardize by titrating 20 cc. with thiosulfate solution with starch indicator in the manner described later for standardization of thiosulfate against iodate.

The factor for thiosulfate solution is obtained from the following formula:

$$\frac{\text{X cc used}}{\text{cc. of iodine solution}} = \text{factor for the iodine solution}$$

Standard thiosulfate solution (approximately tenth-normal) for standardizing iodine solution. Weigh out 25 Gm. of crystalline sodium thiosulfate, dissolve in distilled water and dilute to 1 liter in a volumetric flask. Standardize by titration against iodate or biiodate solution. To 25 cc. of the standard tenth-normal iodate or biiodate solution in an Erlemeyer flask add about 10 cc. of the 10 per cent solution of potassium iodide and about 20 cc. of normal hydrochloric acid. The thiosulfate is delivered into the acid from a buret. When the iodine color has faded to a pale yellow, 1 cc. of starch solution, prepared as described later, is added and the titration is continued until the blue color of the starch-iodine compound has entirely disappeared.

$$\frac{\text{cc. of tenth normal iodate}}{\text{cc. of thiosulfate}} = \text{factor for the thiosulfate solution}$$

Standard iodate or biiodate solution (tenth-normal) for standardizing thiosulfate solution. Weigh out 3.566 Gm. of potassium iodate or 3.25 Gm. of potassium biiodate, dissolve in distilled water in a 1 liter volumetric flask and dilute to the mark. This solution, if carefully made up, does not need standardization. If kept in a cool place in a glass-stoppered bottle, it will retain its strength almost indefinitely.

Starch solution for iodometric titrations. Rub up 1 Gm. of ordinary corn or potato starch with a little cold water until a suspension has been formed. Pour into 200 cc. of boiling water and boil for a few minutes. Allow the mixture to stand until the sediment has settled. The clear supernatant solution is used as the indicator. Deterioration may be prevented or retarded by adding 1 Gm. of salicylic acid per liter to the water used for preparing the starch solution. Without such addition, it deteriorates within a few days.

Procedure: Five cubic centimeters of blood is drawn from a vein in the arm in the usual manner and without the addition of anticoagulant. After the clot has formed, it is loosened from the sides of the tube, which is then centrifuged. The serum is poured off into a centrifuge tube, and after being again well centrifuged to get rid of any suspended cells it is ready for use. If the determination cannot be done on the day the blood is taken, the blood should be preserved in the refrigerator over night. The results obtained on serums before and after twenty-four hours' preservation in the refrigerator agree closely.

Place 10 cc. of buffer substrate at p_H 5 (no. 1) in each of two test tubes. Allow the tubes to remain in a water bath at 37.5 C. for five minutes or more. Without removing the tubes from the bath, add exactly 0.5 cc. of serum to each, stopper, mix and allow to remain in the bath exactly thirty minutes. At the end of this time add at once 4.5 cc. of diluted phenol reagent (no. 2), mix and filter.

In each of two test tubes place 10 cc. of buffer substrate at p_H 5 (no. 1). Add to each 0.5 cc. of serum and at once 4.5 cc. of diluted phenol reagent (no. 2) and filter. These tubes serve as controls. Pipet 10 cc. of filtrate from the test and control solutions into clean test tubes. Add 2.5 cc. of 20 per cent sodium carbonate solution, mix and replace tubes in the water bath for five minutes to bring up the color.

Compare in the colorimeter with a standard made up at the same time by adding 2.5 cc. of 20 per cent sodium carbonate solution to 10 cc. of phenol solution and reagent (no. 5). Place the unknown solution on the left side of the colorimeter and set at 30 mm. Place the standard on the right side and match the colors. Huggins and Hodges prefer the use of an Evelyn photoelectric colorimeter using 6000 Å filter.

Calculation: The phosphatase activity of the serum is expressed as King-Armstrong units per hundred cubic centimeters of serum and is numerically equal to the milligrams of phenol which would be set free from the phenyl phosphate under the standard conditions by 100 cc. of serum. Thus, units of phosphatase per hundred cubic centimeters equals milligrams of phenol per hundred cubic centimeters of serum in the test tubes minus milligrams of phenol per hundred cubic centimeters of serum in the control tubes. The number of milligrams of phenol in 100 cc. of serum in the test tubes and in the control tubes is found by the equation:

$$\frac{\text{Reading of the standard}}{\text{Reading of unknown}} \times \text{strength of standard} \times \frac{15}{10} \times \frac{100}{0.5}$$

With the unknown solution set at 30 mm. and the strength of standard equal to 10 mg. per hundred cubic centimeters, all figures in this equation cancel out, making it equal to "reading of standard." More simply, then, the units of phosphatase per hundred cubic centimeters equals reading of standard (against the test) minus reading of standard (against the control).

RESULTS

Table 2 is a record of the determinations of phosphatase made according to Huggins' modification of the King and Armstrong method.[48] Again there are two series of determinations for each animal, one series made at the time of operation and the second series after a varying interval of time. Again 2 animals were used in order to allow a control for the determinations made at each time interval.

In this second study a definite rise in phosphatase activity in the blood serum was noted from the third to the seventh day. Corresponding activity took place in the samples of bone and tissue studied from the fourth to the seventh day. Again there was a decline in phosphatase activity in blood serum, bone and tissue on the seventh, eighth and tenth days.

COMMENT

The explanation of the factor responsible for the local reaction of tissue fluids at the site of injury by which they are somehow rendered more alkaline than the hydrogen ion concentration of the blood, allowing increased phosphatase activity and more favorable conditions for deposi-

TABLE 2.— *Determinations of Phosphatase*

Interval	Cat	Date of Operation	Phosphatase, Units per 100 Cc.		
			Serum	Bone	Tissue
3 days	15	5/23/46	2.0	0.7	6.8
	15	5/26/46	2.1	0.9	3.7
	16	5/23/46	1.1	2.1	6.2
	16	5/26/46	2.0	1.2	3.4
4 days	12	5/15/46	1.0	0.8	5.1
	12	5/19/46	2.7	3.5	10.7
	14	5/15/46	1.4	2.3	6.4
	14	5/19/46	2.4	2.8	6.2
5 days	8	5/09/46	1.8	0.9	3.9
	8	5/14/46	2.2	0.9	6.0
	17	5/23/46	1.4	2.1	4.3
	17	5/28/46	3.2	5.1	4.6
6 days	10	5/13/46	2.4	1.6	3.9
	10	5/19/46	1.3	6.5	8.2
	11	5/13/46	1.6	0.8	8.6
	11	5/19/46	2.4	5.1	5.0
7 days	5	4/30/46	0.8	2.3	8.2
	5	5/07/46	0.9	0.5	5.5
	6	4/30/46	1.4	1.3	4.1
	6	5/07/46	1.6	0.8	4.6
8 days	3	4/24/46	1.1	2.5	7.0
	3	5/02/46	0.7	1.2	2.2
	4	4/24/46	1.1	1.7	5.2
	4	5/02/46	1.3	0.6	7.3
10 days	1	4/22/46	0.8	2.6	9.7
	1	5/02/46	1.6	0.4	5.8
	9	5/09/46	3.0	1.9	5.3
	9	5/19/46	3.8	1.1	4.7

tion of calcium salts, remains an enigma. Leander[49] stated that regeneration of bone takes place as a result of some specific bone-forming substance activating the nonspecific mesenchymal tissue.

The phosphatase enzyme may be confronted locally by an inhibitor, with retardation of its physiologic action. Inhibitors have been isolated for certain digestive proteases, such as the gastric pepsin and the pancreatic trypsin. Wilkins and Regen[50] have shown that roentgen ray irrad-

49. Leander, G.: A Study of Bone Regeneration, Surg., Gynec. & Obst. **67**:705-714, 1938. Spemann, H.: Experimentelle Beiträge zu einer Theorie der Entwicklung, Berlin, 1936; cited by Leander.

50. Wilkins, W. E., and Regen, E. M.: The Influence of Roentgen Rays on the Growth and Phosphatase Activity of Bone, Radiology **22**:674-677, 1934.

iation of the radiuses of dogs was followed by a decrease in phosphatase activity beginning a few days after roentgen exposure; the activity reached a minimum within one to three weeks and showed a tendency toward normal within four to five weeks. In addition to increased phosphatase activity in an alkaline medium (p_H 9.1), Gutman and his associates[51] found markedly increased phosphatase activity in an acid medium (p_H 5.0) in bone at the site of osteoblastic metastasis secondard to prostatic carcinoma, and metastatic tumor cells arising from carcinoma of the prostate gland apparently retain their capacity to elaborate the phosphatase active in an acid medium found by Kutscher and Wolbergs[25] in normal prostatic tissue. Phosphatase activity, though lessened in degree, was found in this study (figs. 6, 7 and 8) throughout the first six days after production of the bone defect, and on the seventh day there was a striking increase. It is regrettable that the hydrogen ion concentration was not ascertained at the time the various specimens of bone and tissue were secured, and further experiments of such character appear indicated. It is suggested that some factor operating to neutralize the effect of this assumed inhibitor of the phosphatase enzyme may coincide with the process of ionization and precipitation of calcium salts in the connective tissue stroma in the perivascular areas. That the phosphatase activity in the blood serum on the seventh day was not as pronounced as that occurring in the bone and tissue may be explained by the observation of Flood and his co-workers,[46] who determined that urinary secretion of serum phosphatase is found in the cat after ligation of the common duct, as contrasted with the rise regularly observed in man and in the dog, whose kidneys appear to be impermeable to phosphatase.

This study has raised many problems which are worthy of further investigation. The series of experiments has been carried out under conditions that by choice prevented bony union at the site of the defect. A similar study repeated in the presence of a simple fracture and allowing healing to occur would prove of interest. It would be advisable to determine whether there is any phosphatase activity in the bone and tissues at a distance from the site of the bone defect. In the condition of progressive myositis ossificans a clinical opportunity exists for further study of the phosphatase activity in the tissues locally.[53] The local effect of

51. Gutman, E. B.; Sproul, E. E., and Gutman, A. B.: Significance of Increased Phosphatase Activity of Bone at the Site of Osteoplastic Metastases Secondary to Carcinoma of the Prostate Gland, Am. J. Cancer **28**:485-495, 1936.

52. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, Ztschr. f. physiol. Chem. **236**:237-240, 1935.

53. Burrows, H. J.: A Case of Progressive Myositis (Fibrositis) Ossificans, Proc. Roy. Soc. Med. **26**:1330-1334, 1933. Wilkins, W. E.; Regen, E. M., and Carpenter, G. K.: Phosphatase Studies on Biopsy Tissues in Progressive Myositis Ossificans, with Report of a Case, Am. J. Dis. Child. **49**:1219-1221 (May) 1935.

trauma of the soft tissues on the phosphatase activity, without bone defect, would be of interest. Botterell and King[20] reported that the introduction of phosphatase into the site of experimental fractures in rabbits produced no change in the rate or in the apparent quality of the calcification of the bone matrix. Robison and Soames[54] have shown that while calcification in vitro may occur in solutions of inorganic salts supersaturated with respect to the bone salt it will also take place with lower concentrations of calcium and inorganic phosphorus if phosphoric esters are also present, even in small amount. Experiments would appear indicated to determine some suitable menstruum for phosphatase which would hold the enzyme at the fracture site and prevent the rapid absorption through the blood stream which would be expected as a result of the hyperemia secondary to the trauma producing the fracture. Subjecting this menstruum containing phosphatase to variations in hydrogen ion concentration might prove of value in influencing the rapidity of the process of bone repair.

It remains to be emphasized that the experiments performed have been carried out on a relatively small number of animals. The possibility of errors in technic may not be overlooked, although every effort was made to follow the methods described by Bodansky for the actual determinations and the study was made with a minimum in variations of the routine followed. Future experimentation remains indicated to corroborate the essential findings of the study.

SUMMARY

1. A review of the complicated series of events in the process of bone repair has been made.

2. A survey of the enzyme phosphatase and its activity has been reported.

3. The phosphorus content and phosphatase activity in blood serum, bone and tissue at the site of a bone defect was studied in a group of 30 cats, with determinations of phosphorus and phosphatase carried out at the time of operation and at varying intervals thereafter ranging from six hours to ninety days.

4. A decrease in both phosphorus content and phosphatase activity was found to occur on the sixth day in blood serum, bone and tissue after the production of the bone defect.

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54. Robison, R., and Soames, K. M.: The Possible Significance of Hexosephosphoric Esters in Ossification: VII. Calcification in Vitro, Biochem. J. **24**:1922-1925, 1930.

5. The blood serum phosphorus content showed a decided rise on the seventh day after production of the bone defect; otherwise its fluctuation was comparatively mild throughout the course of the experiments.

6. There was only mild increase in the phosphorus present in the bone except for the decrease noted on the sixth day after production of the bone defect.

7. A rise in phosphorus content in the tissues was found on the second day. Decrease in phosphorus content was found on the sixth day and from the twelfth to fourteenth days, a result anticipated because of the local demand on the tissues coincident with the process of ionization and deposition of calcium salts.

8. The phosphatase activity in the blood serum, after a rise on the fifth day, showed a decrease on the sixth day. Activity remained sustained through the seventy-fifth day, with a decrease noted between the fourteenth and forthy-fifth days.

9. The bone phosphatase showed initial activity on the fourth and fifth days. This was followed by a decrease on the sixth day, then a recurrence of activity reaching its height on the twelfth day and continuing well sustained throughout the remaining period of observation.

10. The phosphatase activity in the tissues was found to be increased as early as the twelfth hour, and then it subsided, to recur on the fifth day. There was a decrease on the sixth day. The greatest activity was found on the fourteenth and seventy-fifth days.

11. A discussion of the results of the study has been presented, together with suggestions for further investigation of the activity of the phosphatase enzyme.

12. Phosphatase activity in blood serum, bone and tissue was studied in 14 additional cats, King and Armstrong's method of determination being used, with results corresponding to those in the original group of 30 cats.

SOLITARY (UNICAMERAL) BONE CYST

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IN 1934 Coley and Higinbotham,[1] of New York Memorial Hospital, reviewed the subject of solitary bone cyst and presented 26 cases that they had personally observed from 1920 to 1933. The present communication covers another 26 cases of solitary bone cyst observed at Memorial Hospital from 1933 to 1946. An attempt is made to compare the data collected in these two periods.

CLINICAL FEATURES

Solitary bone cyst generally attracts attention during the first and second decades of life. It usually occurs in the proximal part of the metaphysis of a long bone, the humerus being the bone most commonly involved. A history of trauma at the onset of symptoms is often obtained from the patient. The symptoms are ordinarily mild until a pathologic fracture occurs. Objective findings on physical examination are meager and nonspecific. Slight tenderness may be present over the cystic area. Some limitation of motion may be present because of pain. The diagnosis is made from the roentgenograms. These show the area of bone destruction located on the diaphysial side of the epiphysial line. The circumscribed area of radiolucency is surrounded by an expanded and attenuated cortex. Often there may be fine trabeculations. The trabeculae do not represent actual partitions of the cavity but rather ridges on the wall of the cyst.

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1. (*a*) Coley, B. L., and Higinbotham, N. L.: Solitary Bone Cysts, Ann. Surg. **99**:432-448 (March) 1934. (*b*) Jaffe, H. L., and Lichtenstein, L.: Solitary Unicameral Cyst with Emphasis on Roentgen Picture: Pathologic Appearance and Pathogenesis, Arch. Surg. **44**:1004-1025 (June) 1942.

CAUSATION

The cause of solitary bone cyst is not known. Several theories have been advanced, but they all lack supportive evidence. These theories shall be mentioned but briefly in this paper. A discussion concerning them may be found elsewhere.

1. Traumatic theory. This theorizes that there is a traumatic hematoma which is not absorbed and which becomes the site of the cyst.

2. Theory of Inflammation. This theorizes that the cysts are the end result of a low grade infection.

3. Metabolic theory. This is based on the theory that cysts are the result of a faulty calcium metabolism.

4. Abnormal hyperplasia of osteoclasts. This presupposes trauma and disturbed circulation in a subcortical area and accounts for cystic formation as a result of an unequal balance between osteoclastic action and repair of bone.

5. The theory that bone cysts represent central bone tumors which have undergone cystic softening.

PATHOLOGIC PROCESS

At the time of operation no evidence of disturbance can be noted extraperiosteally unless there has been a recent fracture, and then there will be hemorrhagic discoloration of the surrounding tissues. The cortex over the cyst is so thin that it is easily incised while the operator is cutting through the periosteum. The cortical window can easily be cut with an ordinary pair of dissecting scissors. The cyst usually contains a yellowish or serosanguineous fluid. Examination of the inside of the cyst reveals an irregular cavity. The walls show many ridges but none sufficiently raised to divide the cavity. It is lined with a smooth, thin connective tissue membrane.

Microscopic examination[1b] shows the thin cortical wall of the cyst to be composed of rather loose-meshed osseous tissue. This represents a new cortex which has been slowly laid down by the periosteum as the old cortex was being resorbed. The fairly large vascular spaces of the cortical shell usually reveal many dilated and thin-walled vessels. On the walls of these spaces a scattering of osteoclasts may be seen, and some osteoclasts may be present also between the periosteum and the outer surface of the cortical shell on the one hand and between its inner surface and the lining membrane on the other. The lining membrane may be composed essentially of rather vascular connective tissue. It may also show a scattering of blood pigments, either free or within phagocytes. Here and there in the lining membrane some osteoid and osseous trabeculae may be seen

to have formed through metaplasia. The bits of tissue which are usually found adherent to the lining of the cyst will appear on microscopic examination to be mainly fibrin clots, often containing some red blood cells and undergoing organization and even calcification and ossification.

SUMMARY OF DATA

Sex.—Fifteen of the patients were males, and 11 were females. This is the same sex distribution as was noted in the previous report thirteen years ago.

Age.—This is essentially a disease of the young. Nineteen of the 26 patients were under 20 years of age. The average age was 14.7 years.

Bone Involved.—Seventeen of the cysts occurred in the humerus; with two exceptions these were at the proximal ends. In 11 cases the right humerus was involved and in 6 the left. The femur was the next most common site. In 4 cases the cyst occurred in the proximal end of the femur and 1 in the distal end. In the other 4 it occurred in a rib, in the ilium, in the tibia or in the ulna.

Trauma.—Ninteeen of the 26 patients gave a history of trauma at the onset of symptoms. Of these 11 had pathologic fractures either at the onset of symptoms or at the time of admission to the hospital. The cyst is usually well advanced before its presence is known, and only slight trauma is required at the time to produce a pathologic fracture.

Symptoms.—Pain was the most constant complaint. In a few cases there had been a previous fracture with complaint of "swelling" or "presence of a cyst" on admission to the hospital. The symptoms persisted for from one week to thirty months before admission.

Treatment.—The treatment was surgical in all cases with the exception of 1, in which no active treatment was carried out. Simple curettage was performed in 11 and curettage plus bone transplantation in 14 cases. The bone transplant was in the form of either bone chips or a large cortical graft. Rib resection was performed in 1 case.

Recurrences took place in 4 cases. In case 1 curettage and a transplant of a graft from the right tibia was performed for a simple cyst in the left humerus. A recurrence followed, and about one year later the cyst was again curetted and bone chips removed from the tibia were placed in the cavity.

In case 6 three surgical procedures were required. The patient presented a solitary cyst in the upper part of the left humerus. At first curettage with zinc chloride cauterization was carried out. About one year later a second operation was necessary. At this time the cyst was again curetted, and a bone graft was transplanted from the left tibia.

There was again evidence of a recurrence, and two years after the second operation the cyst was curetted and bone chips were inserted in the cavity. The area healed well after the third surgical procedure.

The patient in case 26 presented a solitary cyst in the middle of the right humerus. At the first operation the cyst was curetted and a graft transplanted from the left tibia. Three years later there was evidence of recurrence. At that time the cyst was again curetted and another graft was transplanted from the left tibia. Two years later he had evidence of recurrence. At this time the entire mid-portion of the right humerus was resected and a large graft was placed between the proximal and distal remaining portions of the humerus (fig.2).

In a fourth case, case 21, there was a recurrence four years after a solitary cyst in the upper part of the right humerus had been curetted and a graft applied. Operation has again been recommended but not yet performed.

The treatment in the present series was different in certain respects from that used in the group of 26 cases reported thirteen years ago. In 8 of those cases the patient received some form of radiation therapy, whereas in none of the present series was irradiation carried out.

REPORT OF TWENTY-SIX CASES

CASE 1.—E. V., a boy aged 10 years, was admitted to Memorial Hospital on June 14, 1942, with a history of having fallen on his left shoulder three months previously. The next day a roentgenogram showed a fracture through a bone cyst. The chief complaint on admission was swelling of the left arm. The roentgenographic diagnosis was bone cyst, with pathologic fracture. Curettage of the cyst with transplant of a graft from the right tibia was performed on June 17. The pathologic findings were consistent with the diagnosis of bone cyst. There was evidence of a recurrence a few months later, and on May 10, 1943, the cyst was again curetted and bone chips removed from the tibia were placed in the cavity. Roentgenograms three years later still revealed a small cavity which did not show signs of healing.

CASE 2.—C. M., a girl aged 9, entered Memorial Hospital on June 2, 1941. In December 1940 she injured her right shoulder when she fell downstairs. The roentgenographic diagnosis was bone cyst, with no evidence of fracture. Curettage of the cyst with transplant of bone from the left tibia was performed on June 4. There were rapid healing and regenerations, with resulting excellent function of the arm.

CASE 3.—M. H., A boy aged 12, was admitted to Memorial Hospital on Oct. 15, 1941, with a history of having fallen on the ice in March 1939 and injured his left shoulder. At that time a fracture was demonstrated through a cystic area in the left humerus. He continued to have some pain in that area even after it had healed. The roentgenographic diagnosis on admission was bone cyst, inactive stage. Curettage of the cyst was performed on Oct. 17, 1941. There was good healing, and the function was excellent after this procedure.

CASE 4.—P. G., a man aged 23, entered Memorial Hospital on Jan. 24, 1936, with the history that three months previously he had slipped and fallen on a damp floor. About one week later he noticed a dull aching pain in the region of the right greater trochanter. Roentgenograms showed a solitary bone cyst at least 10 cm. in length below the lesser trochanter of the right femur. On Jan. 28, 1936,

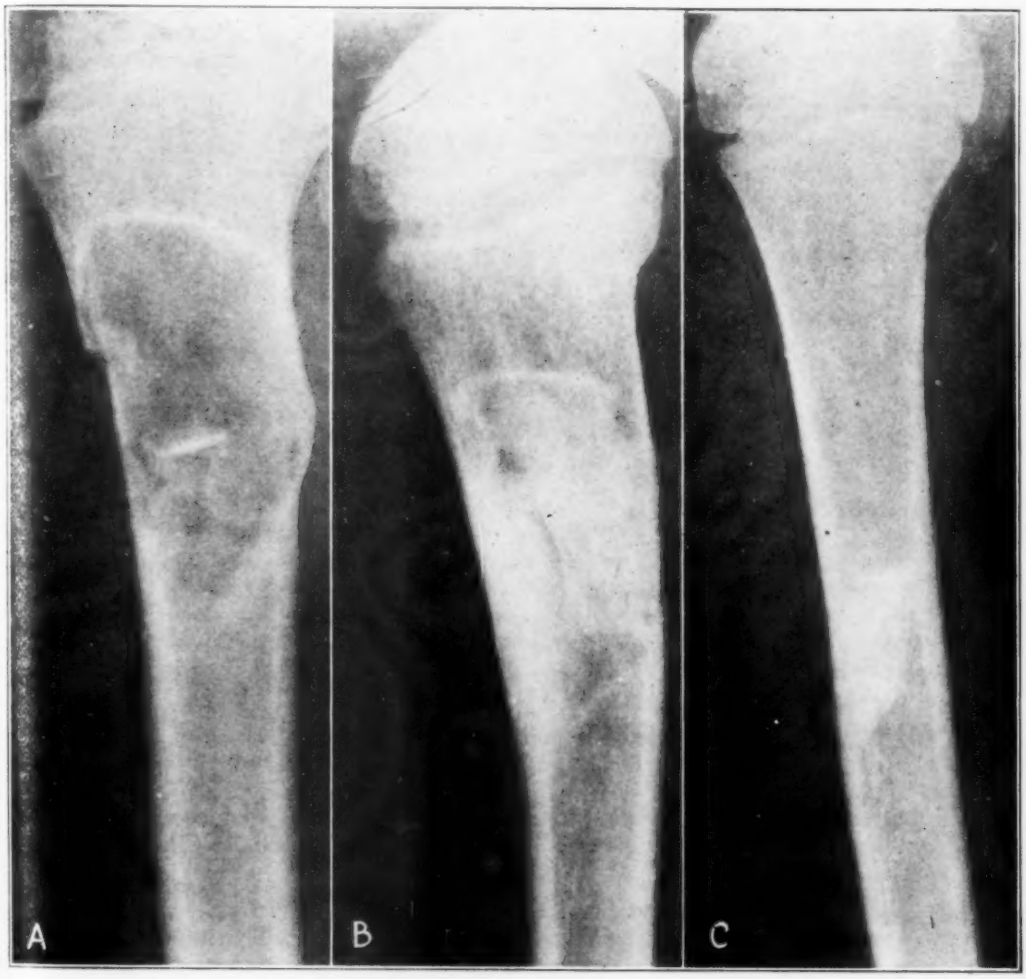

Fig. 1.—*A*, unicameral bone cyst, with pathologic fracture in case 7. *B*, result three months after curettage and the use of the cortical window as a graft. *C*, final follow-up roentgenogram taken four and a half years after operation.

the area was curetted. The roof of the cyst was placed in the curetted cavity, but no other graft was used. There was excellent healing, and good function returned.

CASE 5.—I. F., a boy aged 13, was admitted to Memorial Hospital on Feb. 28, 1938, with the history that five days previously, while throwing a ball, he had suddenly experienced pain in the right arm. Roentgenograms showed a cystic

process in the upper end of the humerus. On March 2 the cyst was curetted and cauterized with zinc chloride solution. The functional result was good postoperatively. Six years later roentgenograms disclosed a recurrence of the cyst.

Case 6.—J. D., a girl aged 3, was admitted to Memorial Hospital on Oct. 2, 1940. The patient fell and struck her left arm about ten days before her admission. Roentgenograms were interpreted as showing a bone cyst or a giant cell tumor involving the upper third of the left humerus. On October 5, the cyst was curetted and cauterized with zinc chloride solution. Postoperative roentgenograms revealed a recurrence of the cyst. In September 1941 the child fell on her left arm and fractured it through the cystic area. On September 18, the cyst was again curetted; a bone transplant was obtained from the left tibia and placed in the defect. Later roentgenograms again showed a recurrence, and on Oct. 28, 1943, a third operation was performed. The cyst was curetted, and bone chips were placed in that area. Excellent function resulted, and no evidence of a recurrence was noted three years after the last operation.

Case 7.—E. B., a boy aged 7, was admitted to Memorial Hospital on Nov. 4, 1940. Four days before the child had fallen down a flight of stairs and injured his right arm. Roentgenograms showed a bone cyst of the upper part of the right humerus, with pathologic fracture. Curettage of the cyst was performed on November 6. The roof of the cyst was implanted into the cavity as a graft. Pathologically, the curetted material resembled a traumatic bone infarct. The healing and the functional results were excellent. (fig. 1).

Case 8.—F. D., a girl, aged 10, entered Memorial Hospital on Aug. 8, 1937. About one month previously pain of unknown origin had developed in the left arm. Roentgenograms showed a bone cyst in the upper part of the left humerus. On August 11 the cyst was curetted and cauterized with zinc chloride solution. Pathologically, some areas resembled a giant cell tumor and others an osteochondroma. There was excellent function postoperatively, but a small cystic area has persisted.

Case 9.—H. K., a boy aged 8, was admitted to Memorial Hospital on Dec. 6, 1943, with the history that thirteen months previously he had sustained a fracture of the right humerus while throwing a ball. He was referred to the Memorial Hospital by another hospital for treatment of a bone cyst in the right humerus. Roentgenograms substantiated the diagnosis, and on December 9 the cyst was curetted and the cavity was filled with bone chips obtained from the left tibia. Aantomic and functional results were excellent.

Case 10.—V. S., a boy aged 13, was admitted to Memorial Hospital on Feb. 2, 1944. He had had a pathologic fracture of the left humerus in March 1942. In July 1943 the left arm was injured and again fractured. Roentgenograms showed a bone cyst. On Feb. 3, 1944, the cyst was curetted and the cavity filled with a graft from the right tibia. The postoperative course was complicated by a gauze sponge which was left in the wound; this was finally removed. Excellent anatomic and functional results followed.

Case 11.—P. G., a girl aged 14, was admitted to Memorial Hospital on Feb. 9, 1944, with a history of having stumbled and bruised her hip eight months previously. She continued to have pain in her left thigh. Roentgenograms showed an irregular area of bone destruction in the left ilium and pubis. Curettage of the cyst was performed on February 11. The pathologic findings were consistent with the diagnosis of bone cyst. Excellent healing and function resulted.

CASE 12.—F. P., a boy aged 7, was admitted to the Memorial Hospital on Oct. 19, 1942. Three months prior to admission the mother noticed that the boy limped on the left lower extremity. Roentgenograms showed a cleancut area of bone absorption in the intertrochanteric area of the left femur. On October 21, the cyst was curetted and a bone graft obtained from the left tibia was placed in the curetted area. Good healing and excellent function resulted.

CASE 13.—M. G., a boy aged 3, was admitted to the Memorial Hospital on July 23, 1941. About ten days previously the child fell on his left arm. After this it was noticed that he favored that arm. Roentgenograms showed a bone cyst in the left humerus. On July 24 the cyst was curetted and a bone graft was transplanted from the right tibia. Pathologic studies of the curetted material revealed productive osteitis. There was good regeneration of bone, and good function resulted.

CASE 14.—T. L., a boy aged 4, was admitted to Memorial Hospital on Jan. 28, 1941. In May 1940 the child fell on the beach; after this he seemed to favor the right arm. Roentgenograms at that time showed a pathologic fracture through a cyst in the right humerus. He was observed at intervals by the orthopedic surgeon in charge, and follow-up roentgenograms were taken. He was referred to Memorial Hospital because the area was becoming larger. On Jan. 29, 1941, the cystic area was curetted and a bone graft obtained from the left tibia was placed in the defect. There was good regeneration of bone. Functional results were excellent.

CASE 15.—C. C., a man aged 45, entered Memorial Hospital on Jan. 29, 1934, with the history that one month previously, while sparring with his son, he received a blow on the lateral aspect of the lower end of the right ulna. This was followed by persistent pain. Roentgenograms of the right forearm showed a healed pathologic fracture through a bone cyst in the middle third of the ulna. The patient was followed at irregular intervals for four years. During this time he was symptom free. Roentgenograms showed increasing calcification in the cyst area. Operation was not performed.

CASE 16.—J. E., a girl aged 6, was admitted to Memorial Hospital on Sept. 23, 1940. One year before her admission she had fallen and injured her right arm. Roentgenograms revealed a bone cyst at the upper end of the right humerus. On September 25 curettage and a transplant of tibial bone were performed. The microscopic observations were consistent with the diagnosis of a bone cyst. There was a recurrence of the cyst after four years. Reoperation was advised.

CASE 17.—W. G., a boy aged 11, was admitted to Memorial Hospital on Nov. 18, 1937. Two months previously he had injured his right thigh when he fell off a swing. The pain persisted. Roentgenograms showed a cystic area in the right femur about 5 inches (12.7 cm.) above the condyles. On November 19 the cyst was curetted and cauterized with zinc chloride solution. Excellent anatomic and functional results followed.

CASE 18.—P. J., a woman aged 28, entered Memorial Hospital on Nov. 5, 1940. Two years previously a roentgenogram of the chest, taken because of a severe cold, revealed a tumor in the area of the tenth right rib. She was given roentgen therapy elsewhere, the details of which are not known. On November 6 the right tenth rib was resected. The pathologic diagnosis was localized osteitis fibrosa. She presented no other symptoms during a five year follow-up.

CASE 19.—M. S., a woman aged 26, entered Memorial Hospital on June 21, 1936, complaining of a dull, aching sensation of the right arm at intervals during

the past nine years. Roentgenograms revealed a large cystic area in the upper portion of the right humerus. On June 24, 1936, the cystic area was curetted and cauterized with zinc chloride solution. Excellent anatomic and functional results followed.

CASE 20.—S. F., a man, aged 30, entered Memorial Hospital on Nov. 19, 1945, with the history of a residual dull pain in the region of the right thigh

Fig. 2.—*A*, roentgenogram in case 26 taken on the patient's admission to the hospital, showing a large cyst with a pathologic fracture. *B*, the recurrent cyst after it had been treated twice by curettage and by application of bone graft. *C*, three months after the mid-portion of the humerus was resected and replaced by a tibial graft.

following a fall on the ice. Roentgenograms showed a cystic area of bone destruction in the upper portion of the right femur. On November 21, the cyst was curetted and cauterized with zinc chloride solution and a large bone graft was transplanted from the right tibia. A caliper splint was worn after the operation. Good function and healing resulted.

CASE 21.—S B., a boy aged 13, was admitted to Memorial Hospital on Dec. 9, 1936, with a pathologic fracture of the right arm which followed the throwing of a football six days previously. He had had an occasional stabbing pain in the right arm on exercise for the year before that. Roentgenograms showed an extensive cystic process in the upper portion of the right humerus, with a fracture at its lower portion. On December 17 a curettage of the cyst was performed and a graft transplanted from the left tibia. Excellent healing and function followed.

CASE 22.—F. B., a girl aged 10, was admitted to Memorial Hospital on Oct. 5, 1933, with a history of pain in the right arm following a fall sustained one month previously. Roentgenograms showed a cyst in the upper portion of the humerus, with possible pathologic fracture. The clinical diagnosis was osteitis fibrosa cystica localisata. On October 11 the cyst was curetted and cauterized with zinc chloride solution. The pathologic diagnosis was bone cyst surrounded by areas of fibrosing osteitis. The postoperative healing was excellent. The functional result was extremely good as observed during a five year follow-up.

CASE 23.—C. P., a girl aged 4, was admitted to Memorial Hospital on Feb. 18, 1936, for treatment of a cyst in the left tibia. No history of trauma was given. The child had no discomfort on admission and had no complaints. Roentgenograms showed a large expansile cystic lesion in the lower part of the left tibia. On February 19 the cyst was curetted and cauterized with zinc chloride solution. Excellent anatomic and functional results followed.

CASE 24.—B. M., a girl aged 9, was admitted to Memorial Hospital on March 24, 1934, with a history of having bruised her right thigh when she fell eight months previously. About four months later she had begun limping. Roentgenograms showed an irregular cystic lesion in the upper portion of the right femoral shaft measuring 8 by 4 cm. On March 28 the cyst was curetted and cauterized with zinc chloride solution. Excellent anatomic results followed. The patient has been asymptomatic during an eight year follow-up.

CASE 25.—M. C., a woman aged 35, entered Memorial Hospital on Nov. 26, 1939, complaining of pain in the right arm. The previous month she had had a routine roentgenogram of the chest taken, and incidental cystic changes were noted in the right humerus. On November 27 the cyst was curetted and a bone graft was transplanted from the left tibia. At operation the cyst was found to contain clear yellowish fluid. The wound and the bone healed well. There was a good functional result, as observed in a three year follow-up.

CASE 26.—D. F., a man aged 31, entered Memorial Hospital on Dec. 27, 1939, with a history of pain in the right shoulder of nine months' duration following a blow on the right arm. Roentgenograms at that time showed a fracture through a bone cyst in the middle portion of the right humerus. A roentgenogram made on his admission to the hospital revealed a cystic desructive lesion in the mid-shaft of the right humerus. On Jan. 3, 1940, the bone cyst was curetted and a graft was transplanted from the left tibia. In 1943 he again complained of pain in the right arm. Roentgenograms showed a recurrence. On June 5, 1943, the cyst was again curetted and another graft was applied from the left tibia. In 1945 and early in 1946 he again had some pain in the right arm, and roentgenograms showed some cystic changes to be present. On April 8, 1946, the midportion of the right humerus containing the cystic area was resected and a graft from the right tibia was placed between the two remaining portions. Anatomic and functional results were good after the last surgical procedure. The pathologic report each time stated that the tissues revealed the presence of bone cyst (fig 2).

COMMENT

Since the advent of the term fibrous dysplasia and its more frequent use in the diagnosis of certain radiolucent bone areas which have in the past been designated as indicative of localized fibrocystic disease, we have encountered bone cysts in the shafts of long bones in adults which lacked some of the features of the unicameral cyst and have been at a loss to explain them on the basis of fibrous dysplasia. There is always the possibility that some of them represent extensive unicameral cysts which have been initiated in early childhood, assumed a more strictly diaphysial location as bone growth has progressed and become stationary, quiescent and partially healed, the healing being by fibrous tissue and not by regeneration of bone. Yet so far there has not been a single opportunity to observe a case which seemed to support this theoretic explanation.

There is great variation in the histologic structure of tissue removed from the cavity of a bone cyst or from its wall. The material may be reported as benign giant cell tumor, or wall of bone cyst, or as indicative of low grade, nonspecific osteitis or rarefying osteitis. Unless the pathologist is familiar with the clinical setting and with the appearance of the roentgenograms, he is not apt to report bone cyst. This adds up to the fact that clinical features and roentgenographic findings are more important than the microscopic appearance in the diagnosis of simple bone cyst.

While 3 instances in which malignant transformation developed in areas treated for bone cyst by roentgen therapy thirteen to fifteen years earlier have been observed by us, we have not encountered this late sequel after surgical treatment. Two of the patients were aged 8 and 1 was aged 10 when given radiation therapy. Two of the cysts were located in the upper part of the humerus, and interscapulothoracic amputation was required in both instances for the sarcoma that ultimately developed. The remaining patient's cyst was in the upper portion of the femur. These cases will be made the subject of a separate report. Other patients with bone cyst treated by roentgen therapy in the past have had ultimate shortening of the limb due to the effect of the radiation on the adjacent growing epiphysis. We have not employed this form of treatment in any of the cases in the present series.

For further details of the operative technic which we employ the reader is referred to the article by Coley and Higinbotham on "solitary bone cyst" and to the one on "surgical treatment of giant cell tumor" by the same authors.[2]

RESULTS

In 1 case pathologic fracture appeared to induce satisfactory regeneration of bone in the cyst. In all the 25 cases in which surgical treatment

2. Coley, B. L., and Higinbotham, N. L.: Surgical Treatment of Giant Cell Tumor, Ann. Surg. **103**:821-835 (May) 1936; footnote 1*a*.

was carried out the postoperative course was uneventful and the wounds healed by first intention. Healing of the cyst-bearing area was satisfactory in 18 cases and was not complete in 2 cases, while recurrence took place in 6 instances. Of the cysts which recurred, 2 have not yet been reoperated on, 2 healed completely after a second operation and 2 recurred after a second operation but have remained healed after a third operation.

It is our impression that patients in whom bone transplants are used to fill the cavity do better than those for whom curettage alone is employed; this seems to us more striking when adults are involved, since the natural regenerative powers of the bone are greater in children.

As a result of our comparison of the present series with the earlier group of comparable size, we have concluded that surgical treatment is the method of choice, and we no longer recommend or employ roentgen therapy for bone cyst.

SUMMARY AND CONCLUSIONS

Solitary (unicameral) bone cyst is relatively rare, since in the past twenty-six years only 52 cases have been observed in an active clinic for the treatment of tumors of bones. It is distinctly a disease of childhood and adolescence and affects the proximal end of long bones, particularly the humerus and the femur.

Treatment is best carried out by surgical measures. These may result in occasional recurrence; reoperation will usually then be successful, but resection and segmental graft may sometimes be required. Complications such as infection of the wound should be nil and results are generally most satisfactory.

Cavities are best filled with bone taken either from the tibia (cortical) or from the iliac crest (cancellous).

Radiation therapy is not recommended because it entails exposure of the epiphysial plate and may therefore affect bone growth. We have seen late untoward results following roentgen therapy given twelve to fifteen years earlier.

In this series there have been no examples of cysts becoming sarcomatous when surgical treatment was used.

MIXED TUMOR OF THE BRIDGE OF THE NOSE

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DAVID GRAYZEL, Ph.D., M.D.
AND
SAMUEL ACHS, M.D.
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IT IS the purpose of this paper to describe a mixed tumor of the skin over the bridge of the nose and to discuss some of the important clinical and histologic features presented.

REPORT OF A CASE

M. W., a 36 year old man, was admitted to the Jewish Hospital because of a small growth over the bridge of the nose, said to have been present for two years. When first observed, the growth appeared as a nodule the size of a pea. It gradually increased in size, and although painless it interfered with the necessary wearing of spectacles.

Examination of the patient at the time of his admission to the hospital revealed an irregular raised nodular deformity over the bridge of the nose of a maximum diameter of 1.2 cm. The skin overlying the nodule was intact and normal in appearance. The nodule was freely movable over the subcutaneous tissues, and it was soft in consistency and nontender. A diagnosis of sebaceous cyst at the nose was made.

With the patient under anesthesia produced by local infiltration of 1 per cent procaine hydrochloride, an incision was made immediately over the tumor into the skin. The tumor shelled out readily from its attachment to the subcutaneous tissues, and the wound was closed with silk sutures.

Grossly, the tumor appeared as an encapsulated nodule which measured 1 cm. in diameter. It was somewhat firm and on section presented a homogeneous gray-white appearance.

Microspocially, the appearance was typical of mixed tumor and seemed to be indistinguishable from that of other mixed tumors of the salivary glands. The tumor was made up of epithelial and connective tissue elements. The parenchyma consisted of epithelial cells which formed a definite structural pattern; they were arranged for the most part in glandlike or ductlike structures. The epithelial cells were of uniform size and formed a single layer enclosing a narrow lumen. The cytoplasm of the cells was clear and often hydropic and swollen. The nucleus was spherical or vesicular, usually centrally placed and rather deep staining, but it showed no evidence of mitosis. In certain areas considerable hydropic degeneration of the cells lining an alveolus could be seen, with a tendency toward small cyst formation. The lumen of such an alveolus was filled with an amorphous,

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granular, pink-staining material. Occasionally the cells were arranged in irregular masses or islands, and often they resembled squamous epithelium. The stroma separating the epithelial structures consisted for the most part of loose myxomatous

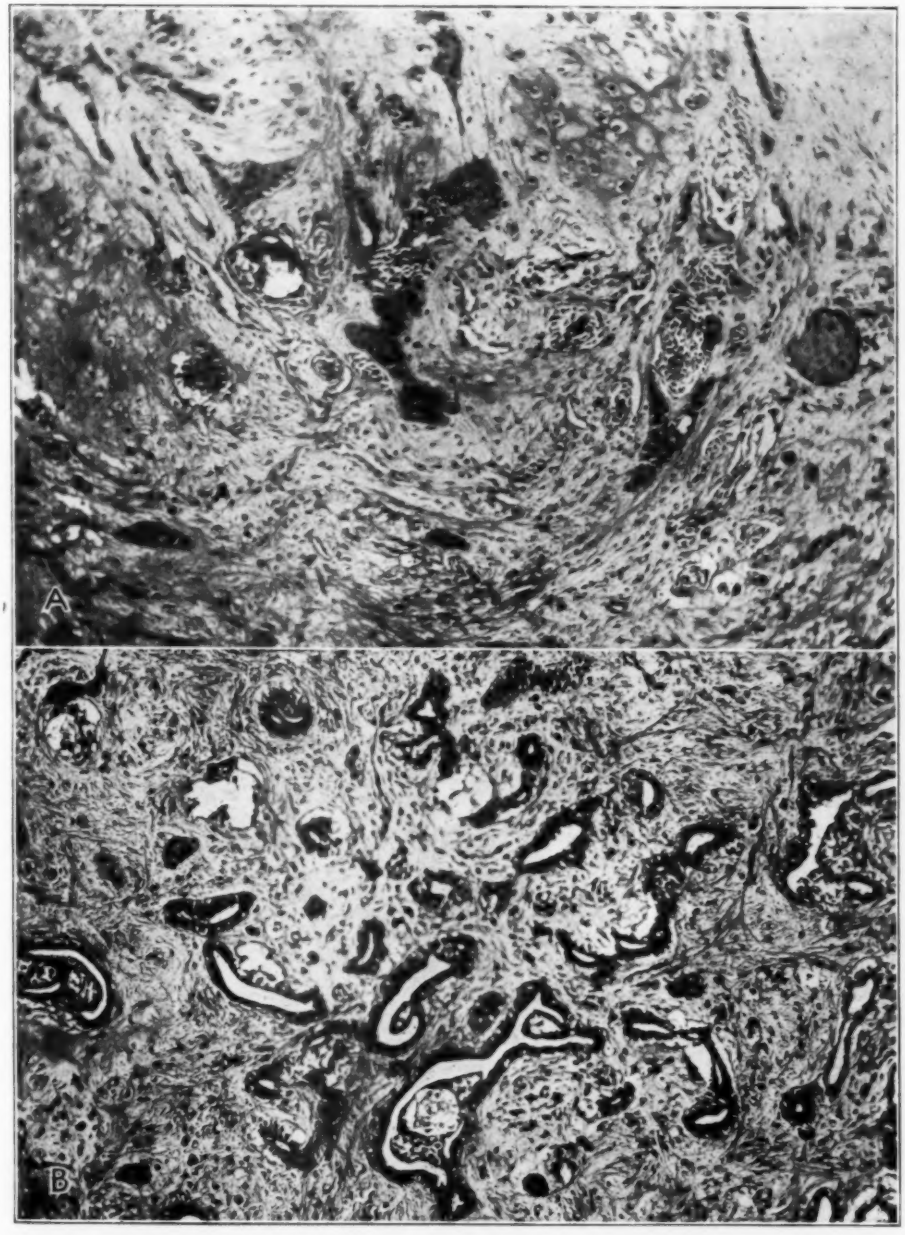

Fig. 1.—*A*, different components making up the tumor. Hematoxylin and eosin; × 90. *B*, alveolar structure in portions of the tumor. Hematoxylin and eosin; × 120.

tissue. The latter was composed of branching triangular-shaped cells embedded in a matrix of homogeneous mucoid substance which stained blue with hematoxylin and eosin. Areas of immature fibrillar cartilage formation could be seen at irregular intervals amidst the myxomatous tissue. Nowhere was there any evidence of transformation of the frank epithelial tissue into myxomatous tissue. The entire tumor was surrounded by a thin connective tissue capsule which was free from any metastasis (figs. 1 and 2).

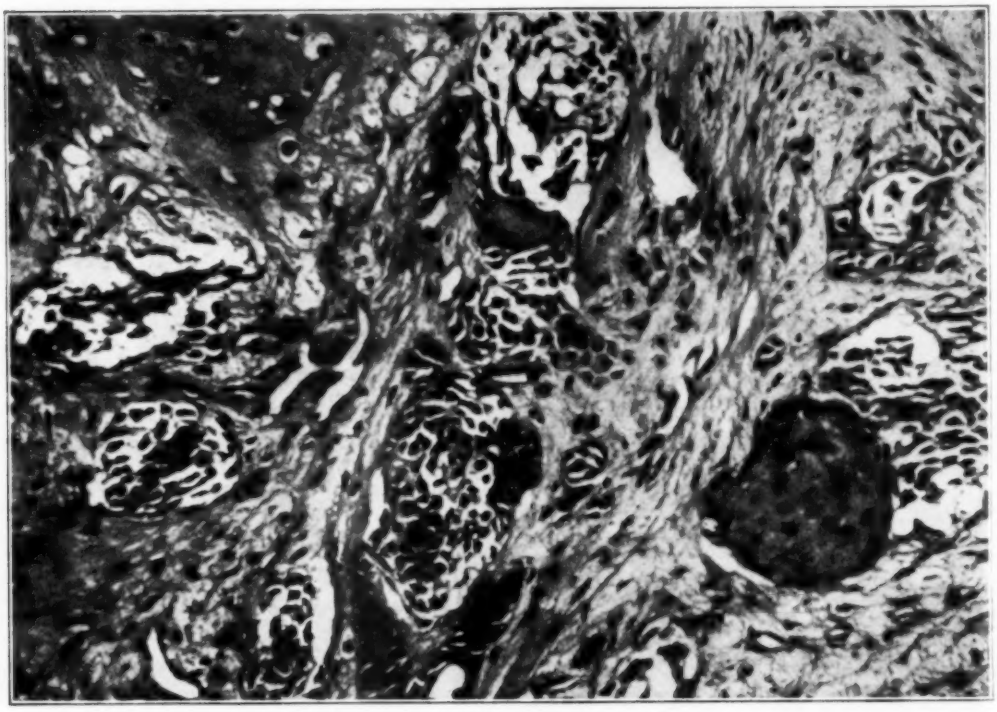

Fig. 2.—Photomicrograph of the tumor under higher magnification. Hematoxylin and eosin; × 300.

COMMENT

Considerable interest has been aroused in recent years regarding the origin and development of mixed tumors of the salivary glands and of the oral-facial region. Few tumors, indeed, present a more variable and more complicated histologic picture than those of the mixed variety, and there is still considerable discussion of their histogenesis. Much of the confusion about the nature of the tumors has arisen from the peculiar myxomatous and pseudocartilagenous nature of the stroma which forms a most conspicuous picture of the growth. The general inclination is to regard these tumors as true epithelial growths without mesodermal elements. The explanation most commonly given is that the myxomatous and cartilagenous components of the stroma are derived by direct trans-

formation of the parenchymal epithelium into this embryonal form of connective tissue. This is believed to be brought about chiefly by the discharge of secretions, mucoid in nature, into the interstices of the stroma. In contrast to this concept is the view that the myxoid, cartilagenous and osseous constituents of the tumor are formed by metaplasia from the connective tissue stroma.

Billroth[1] first advanced the theory that all mixed tumors are essentially of mesenchymal origin, but his theory has been disputed in view of the fact that the parenchyma of the tumor consists unquestionably of epithelial tissue. Sheldon[2] expressed the belief that the connective tissue elements of the tumor are derived by direct transformation from the neoplastic epithelium; this concept is upheld by many other investigators. Hemplemann and Womack[3] were able to differentiate mesenchymal mucus from epithelial mucus by means of special staining technics. They found both these substances to be present in mixed tumors of the parotid gland, and they concluded as a result that two tissue components are represented. They regarded such tumors, therefore, as truly mixed neoplasms. McFarland[4] and Swinton and Warren[5] expressed the opinion that these growths develop as a result of misplaced embryonic cells, probably of branchial cleft origin. From all these conflicting reports, it appears that there is still considerable lack of unanimity of opinion as to the origin of the tumors and the manner of their formation.

While the great majority of mixed tumors are associated with the salivary glands, many of them are known to arise from other locations such as the oral-facial region, especially from the palate, lips, nasopharynx and the skin of the face and scalp. Sanders[6] reported 12 cases of mixed tumors of the lacrimal glands, and Halpert[7] reported 2 cases in which similar tumors arose from the bridge of the nose and the hard palate respectively.

This group of neoplasms has been generally accepted to be a definite clinical and histologic entity and to present cytologic features

1. Billroth, T.: Beobachtungen über der Geschwulste der Schpeicheldrüsen, Virchows Arch. f. path. Anat. **17**:357, 1859.

2. Sheldon, W. H.: So-Called Mixed Tumors of the Salivary Glands, Arch. Path. **35**:1 (Jan.) 1943

3. Hemplemann, L. H., and Womack, N. A.: The Pathogenesis of Mixed Tumors of the Salivary Gland Type, Ann. Surg. **116**:34, 1942.

4. McFarland, J.: Ninety Tumors of the Parotid Region, in All of Which Postoperative History Was Traced, Am. J. M. Sc. **172**:804, 1926.

5. Swinton, N. W., and Warren, S.: Salivary Gland Tumors, Surg. Gynec. & Obst. **67**:1, 1938.

6. Sanders, T. E.: Mixed Tumors of the Lacrimal Gland, Arch. Ophth. **21**:239 (Feb.) 1939.

7. Halpert, B.: Salivary Gland Tumors in Rare Sites: Report of Two Cases, Yale J. Biol. & Med. **5**:469, 1933.

which are common to the entire group, independent of their site of origin. The most highly characteristic tumors are necessarily those which contain reasonably high numbers of all the various types of cells known to form the neoplasm. The tumor is made up essentially of two different types of intimately connected cells. One is epithelial, and the other is identified as being derived from connective tissue because of the morphologic appearance, staining peculiarities and arrangements. The tumor always displays cellular components and structural patterns which form a unique characteristic of the neoplasm and render microscopic diagnosis of the tumor unmistakable.

The histopathologic features presented in our case show two distinct morphologic changes: first, a parenchyma composed of epithelial cells and, second, a stroma composed of myxoid and cartilagenous tissue. The parenchyma of the tumor consisted unquestionably of epithelium which assumed for the most part an alveolar or ductlike structure. On occasions, the epithelial cells formed isolated islands or solid nests and assumed a squamous-like character. The epithelium lining the alveoli formed a single layer of cells of medium height and of uniform shape and appearance. The cytoplasm was relatively clear and sometimes hydropic and swollen, and it contained a single dark-staining nucleus. No mitotic figures could be seen anywhere in the various sections studied, nor was there a tendency for the cells to invade the capsule, lymph or blood stream. In places the epithelial cells were seen to undergo degenerative changes; the cytoplasm became foamy and the nucleus pyknotic. Associated with these degenerative changes in the epithelium lining the alveoli were found also cystic changes within the affected alveoli. There the cystic spaces were filled with an amorphous pink-staining material. The stroma of the tumor consisted essentially of myxoid tissue which closely resembled early, immature, embryonal connective tissue. The connective tissue cells were loose and widely spaced; they were triangular or stellate in shape and possessed numerous delicate threadlike processes. The cells were embedded in a matrix consisting of a mucoid substance and having a fibrillar or granular appearance. Areas of poorly formed and immature fibrillar cartilage could also be seen at irregular intervals within the stroma. The epithelial and connective tissue elements of the tumor were distinct, and in no place could one discern any direct or indirect transition from the parenchyma of the epithelial tissue to the connective tissue stroma. We are of the opinion, therefore, that the different configurations noted in this tumor are separate and distinct entities and not different morphologic phases of growth of the same tumor type. In other words, this tumor is a truly organoid or mixed type of neoplasm composed of two different tissue elements, one epithelial and the other connective tissue. Such a tumor has a dual genetic origin, one in ectoderm and the other in mesoderm.

Evidence of apparent transformation of frank epithelium into myxomatous connective tissue as seen in cases of mixed tumors has been cited by a number of investigators. The concept of such a transformation would presuppose that connective tissue and epithelial tissue, which are of different genetic origins, are interchangeable. It seems incredible that these two different types of tissue of entirely different genetic origins should become interchangeable in the process of tumor formation. Such transformation of cell character has never been found to occur in any other form of neoplasm elsewhere in the body. It also seems most incredible that epithelial cells may undergo such a transformation and assume such a distinct morphologic appearance and tissue pattern that they closely resemble mesenchymal tissue. We are inclined to believe that the various components of a mixed tumor have a dual origin, one epithelial and the other mesenchymal. These various components are closely related and form a unique picture characteristic of an organoid tumor. The relative proportions of parenchyma and stroma in various tumors and sometimes in different parts of the same tumor may vary considerably. In any benign tumor of this type there may be an extremely wide range of structural variation dependent on the frequency of individual cell types and on the growth pattern which such cells seem to follow. At times the epithelial elements may preponderate and form the most conspicuous part of the picture, while at others the connective tissue elements may become most apparent.

Mixed tumors are inherently benign in nature and pursue a slow-growing course. Many, however, are known to recur even after wide excision; in such instances they tend to display malignant characteristics. This is particularly true of tumors arising from the salivary glands. At times these tumors display other features common to malignant growths, namely, rapid and unrestricted growth, invasion of the capsule, lymph and blood stream and metastasis to distant organs.

Little need be said of the prognosis in cases of mixed tumors. Benign growths can be excised successfully in practically all cases, whereas malignant tumors, like those in other locations, permit of only a guarded prognosis. The treatment of choice is surgical and consists of wide excision of the neoplasm. Radiation therapy is of questionable value and should certainly not be employed for benign neoplasms.

DERMOID CYSTS AND TERATOMAS OF THE MEDIASTINUM WITH UNUSUAL FEATURES

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AN EXTENSIVE review of the literature on dermoid cysts and teratomas of the mediastinum was made by Rusby[1], who estimated that 245 cases had been reported up to the end of 1939. An analysis of the cases collected by Rusby indicates that of the patients with dermoid cyst and teratoma of the mediastinum which I have operated on there are 4 who present unusual features.

Rusby stated that it was extremely rare for a dermoid cyst to have a prolongation which extended through the hilus and into the lung and, therefore, to be regarded as partly intrapulmonary. Apparently none of the dermoid cysts which Rusby found described in the literature manifested this type of intrapulmonary extension, but he cited personal communication from Roberts referring to such a case. One of my patients had a dermoid cyst which extended from the mediastinum through the hilus of the upper lobe of the left lung out into the pulmonary tissues.

CASE 1.—One and a half years prior to her admission to Memorial Hospital the patient, a woman aged 21 years, began to cough up bits of white hair. One month before her admission there had been expectoration of blood for three days. The only positive symptoms on physical examination were clubbing of the fingers and rales in the left pulmonary field. Roentgenograms of the chest revealed a mass in the left hilar region (fig. 1). At operation the findings were unusual in that no mediastinal tumor was visible when the left pleural cavity was opened. On palpation of the hilar portion of the upper lobe of the left lung, however, a cystic mass could be felt surrounded by the hilar structures. This mass extended out into the upper lobe, which surrounded it except on the mediastinal side. After dissection of the hilar area the cyst was first exposed. Because a large portion of the upper lobe was occupied by the dermoid cyst and because secondary bronchiectasis had developed, it was necessary to perform a lobectomy together with an excision of the tumor. Because of the pronounced inflammatory reaction in the mediastinum, it was virtually impossible to remove the cyst completely. Postoperatively empyema developed, which required a secondary thoractomy. Although the patient has been clinically well for the past three years, she has on several occasions expectorated a bit of hair, which indicates that the cyst was incompletely removed.

1. Rusby, N. L.: Dermoid Cysts and Teratomata of the Mediastinum: Review, J. Thoracic Surg. **13**:169, 1944.

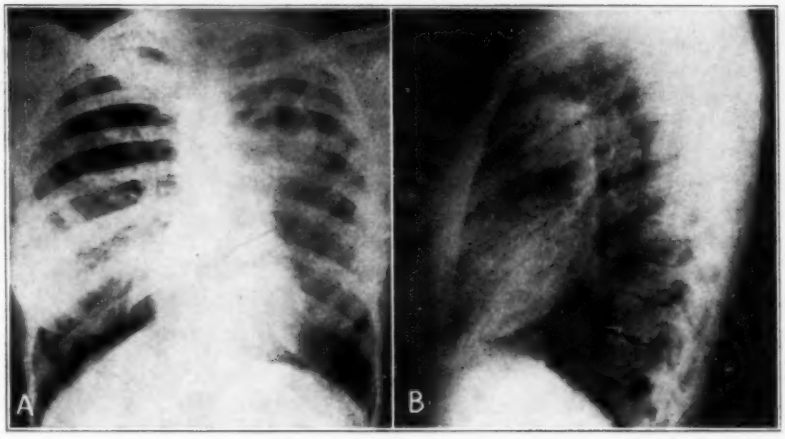

Fig. 1 (case 1).—*A*, posteroanterior view shows tumor mass projecting from the left hilar region. The tumor is roughly spherical in shape. The lower portion appears dense. The upper, radiolucent portion of the cyst was air containing because of a bronchial communication which permitted the evacuation of the sebaceous material and the entrance of air into the dermoid cyst. *B*, lateral view demonstrates that the dermoid cyst lies anteriorly. There is a semilunar air-containing portion in the upper part of the cyst.

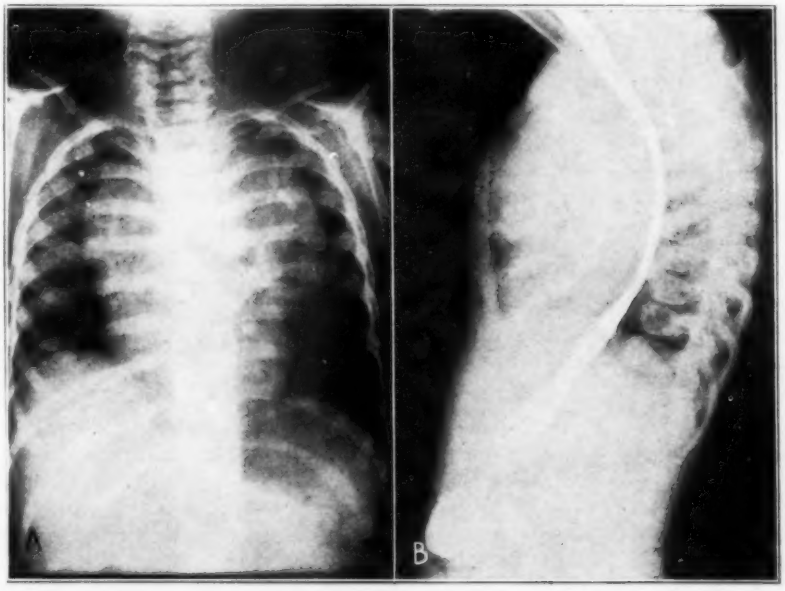

Fig. 2 (case 2).—*A*, roentgenogram demonstrates the huge tumor mass which extends into both pleural cavities to an almost equal degree. *B*, lateral view demonstrates some prominence of the anterior thorax. The tumor extends from the sternum almost to the vertebral bodies and compresses the barium-filled esophagus against the spine.

Comment.—The dermoid cyst, although it arose in the mediastinum, was inseparably associated with the lung, as are some intrapulmonary bronchiogenic cysts. The pulmonary tissues surrounded the dermoid cyst except for the portion which was located in the mediastinum. Because the intrapulmonary inflammatory reaction was not marked, it can be definitely stated that this was a case of intrapulmonary extension of a cyst arising in the mediastinum and not merely an instance of an infected cyst with secondary adherence to the adjacent pulmonary parenchyma.

Although teratomas of the mediastinum result from faulty embryonal development, most of the tumors go unrecognized until adult life because they cause no symptoms for many years. In an analysis of 174 cases in the literature in which the age at the time of diagnosis is given, Rusby found that 17 patients were under 10 years of age. The following case illustrates the huge size which a teratoma of the mediastinum may attain in early childhood.

Case 2.—H. H., a girl aged 4 years, was admitted to Kings County Hospital in October 1942 after a routine roentgenogram of the chest, taken because the mother had tuberculosis, revealed a mediastinal tumor mass. The only symptoms had been occasional dyspnea and fatigue on moderate exertion. On physical examination the child appeared normally developed, although pale; there was prominence of the anterior thorax. There was a large area of dulness in the precordial region, and a harsh systolic murmur was heard over the entire precordium. The trachea was deviated to the right. Roentgenograms revealed a lobulated mass in the anterior portion of the mediastinum projecting into both pleural cavities (fig. 2). A respiratory infection developed shortly after the child's admission to the hospital, and she had some difficulty in breathing at that time. The symptoms disappeared after sulfathiazole therapy. Operation was performed in April 1943. A transpleural approach, with resection of the left fifth rib, was employed. A large lobulated tumor mass was found, which was intimately associated with the mediastinal structures but particularly closely adherent to the pericardium. The tumor was completely removed, and the postoperative course was uneventful. The tumor mass contained large cystic areas. The cavities were lined with stratified squamous epithelium showing considerable keratinization. Thymic tissue was also present within the tumor. The child has developed normally during the three and a half years since operation. Roentgenograms of the chest reveal nothing abnormal (fig. 3).

Comment.—This case illustrates the huge size which an intrathoracic tumor may attain without causing notable symptoms. A superimposed respiratory infection may, however, cause serious respiratory difficulty. Because the tumor extended almost equally into both sides of the thorax, an anterior, midline, sternum-splitting incision had been considered preoperatively, but a transpleural posterolateral incision on the left side was finally decided on. It is clear in retrospect that any type of anterior approach would have been most undesirable. It would not have permitted removal of such a large tumor without unnecessary difficulty. Moreover, the scar of a sternotomy is to be avoided. The flexible nature of the thoracic cage of a child permits removal of a huge tumor after resection of only one rib or through an intercostal incision without division of a rib.

In Rusby's collected series there were 88 dermoid cysts and teratomas which projected toward the right pulmonary field, 63 which were in-

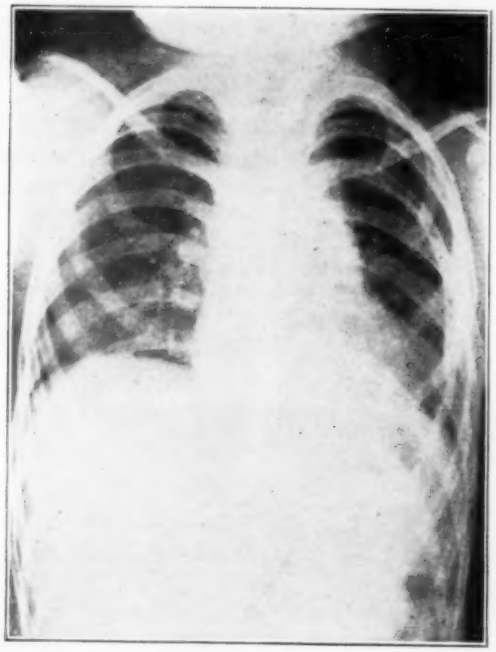

Fig. 3 (case 2).—Roentgenogram taken one and a half years after removal of the huge intrathoracic teratoma. The pulmonary fields appear normal. There has been regeneration of the fifth rib.

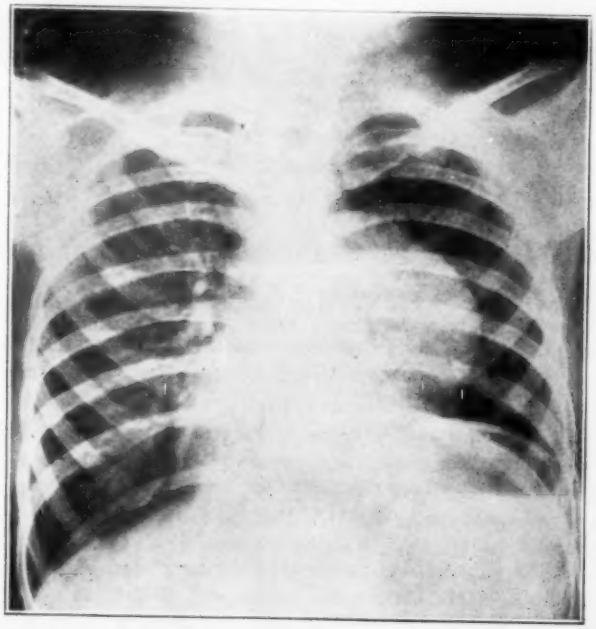

Fig. 4 (case 3).—Roentgenogram taken in 1942, when the patient had completely recovered from an empyema of the left side. A tumor mass is seen projecting from the left side of the mediastinum. No mass is visible in the right side at this time. Note elevation of the left leaf of the diaphragm.

clined toward the left side and 13 which were described as central in position. Although protrusion into both pleural cavities is not rare, the finding of two apparently separate dermoid cysts, one projecting from each side of the mediastinum, is most unusual. In the following case a bilateral dermoid cyst required surgical removal from both sides of the thorax in two stages.

Case 3.—The patient was a girl aged 11 years. In 1941, when she was 7 years old, she was hospitalized for a nontuberculous empyema, which was successfully treated by intercostal drainage. Roentgenograms taken at the time the empyema was present showed a homogenous density throughout the left pulmonary field. After subsidence of the empyema, a rounded mass was noted projecting

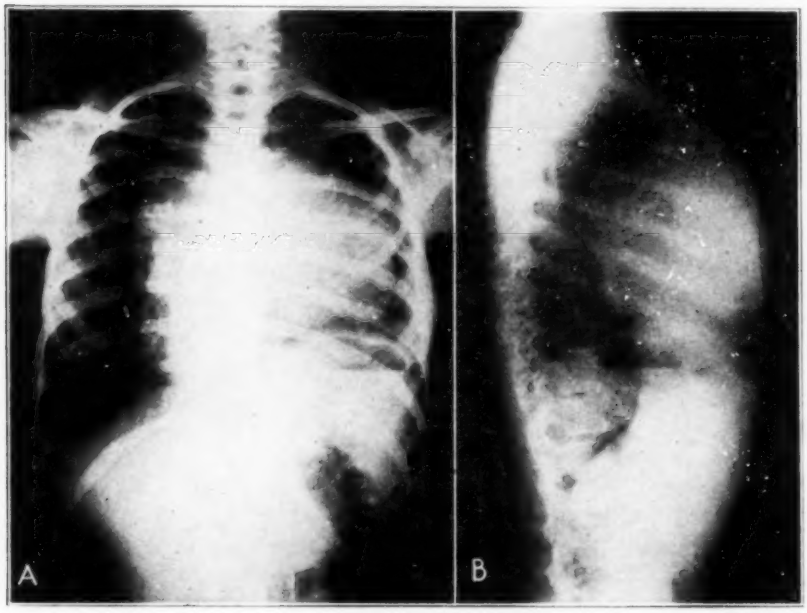

Fig. 5 (case 3).—*A*, roentgenogram taken in 1945 shows large mediastinal tumor mass. In addition to the large mass on the left side, a component on the right side is clearly visible. *B*, lateral film shows that the large mass lies anteriorly.

from the mediastinum in the hilar area (fig. 4). The left side of the diaphragm was elevated. A diagnosis of tuberculosis of the mediastinal lmyph nodes was made. During the following three years the mediastinal tumor increased progressively in size and a small mass also became visible on the right side. When the child first came under my observation in 1945 a large mediastinal tumor mass was present (fig. 5). The girl appeared to be in relatively good health although slightly underweight. She had no pain and no cough or other complaints. The positive physical findings were limited to the chest, with dulness and diminished breath sounds over the left anterior thoracic region and displacement of the heart to the right. There was a hyperresonant note over most of the right side of the thorax. A preoperative diagnosis of teratoma of the mediastinum was made. A left transpleural approach

was used and the mass in the left side was removed, but there was considerable difficulty because of the dense attachment of this mass to the mediastinal structures. The tumor was largely cystic, containing thick yellow material. Sections of the cyst wall revealed the inner surface to be partly lined by stratified squamous epithelium with many hair follicles and sebaceous glands. Some areas of the wall of the cyst were denuded of a specific lining. In one of the nodules in the cyst wall rudimentary bronchial tissue was present. The postoperative course was uneventful. In March 1946 operation was undertaken for removal of the mass in the right side, but because of impaired respiratory function when the thorax was opened, the procedure was terminated without the removal of any portion of the tumor. In September 1946 another operation was performed; through a posterolateral incision the mass in the right side was removed. This was also cystic and was similar in appearance to that previously removed from the left side. It lay in front

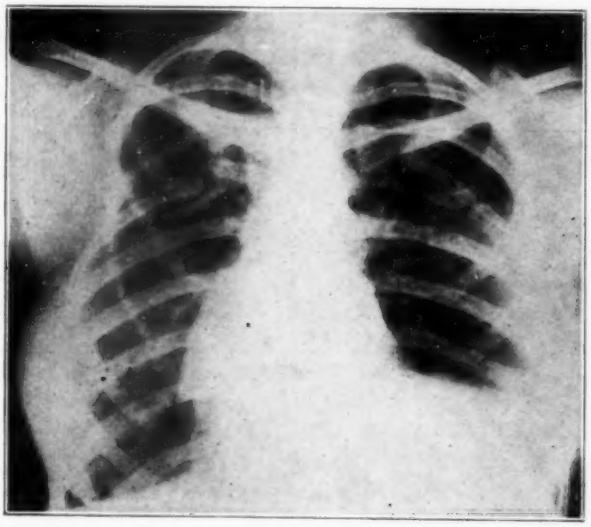

Fig. 6 (case 3).—Postoperative roentgenogram after removal of tumor from both sides.

of the pericardium and the vena cava. It was completely removed, and there was no evidence of any connection with the mass which had previously been taken from the left side. The postoperative course was uneventful. The child has been well since the last operative procedure, and roentgenograms showed good expansion of both lungs (fig. 6).

Comment.—The finding of a separate cyst on both the left and the right side is unique. Before the first operation it was thought that the tumor was probably inoperable because of paralysis of the diaphragm. The involvement of the phrenic nerve, however, was found to be secondary to a chronic fibrous mediastinitis and not due to malignant disease. This illustrates the advisability of exploratory thoracotomy in doubtful cases.

The more complicated the structure of a teratoma of the mediastinum, the greater the possibility of malignant change. But even dermoid cysts may occasionally undergo a malignant process. The presence of much cal-

cification in the wall of a dermoid cyst and the absence of demonstrable enlargement over a period of years do not rule out the possibility of malignant change. The following case illustrates this point.

Case 4.—The patient was a man aged 53 years. Four years prior to his admission to the hospital a roentgenogram of the chest showed a rounded mass in the left side of the anterior mediastinum, with considerable calcification in the outer wall (fig. 7*A*). A diagnosis of dermoid cyst was made, but because the patient was asymptomatic no treatment was recommended by his physician. Roentgenograms of the chest were taken at intervals, and no change in the size of the shadow was noted. In 1944 the patient began to lose weight, and he complained of some weakness and of cough without sputum. A roentgenogram of the chest now showed partial atelectasis of the left lung. There was an area of density continuous with the originally noted mass in the mediastinum (fig 7*B*). The size of the mass delineated by calcification in its walls was unchanged. Bronchoscopy showed extrinsic pressure on the bronchus of the lower lobe of the left lung. An exploratory thoractomy revealed a dermoid cyst which had undergone malignant degeneration.

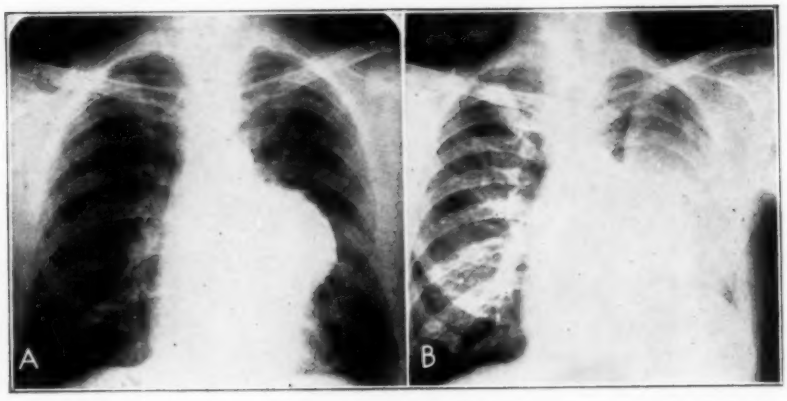

Fig. 7 (case 4).—*A*, roentgenogram taken in 1941 showing sharply demarcated tumor mass with considerable calcification in its outer portion. *B*, roentgenogram three years later shows partial atelectasis of the left lung.

Soft tumor tissue had fungated through the wall of the cyst and had invaded the adjacent mediastinum and the pulmonary hilus. The lesion was inoperable, and only tissue for a biopsy was taken. Postoperatively the patient manifested signs of diffuse metastasis, including subcutaneous nodules. He died three months after exploratory thoracotomy. The tissue removed at the time of operation revealed undifferentiated carcinoma.

Comment.—This case illustrates that even the dermoid cyst with calcified walls which is apparently not changing in size may be undergoing malignant degeneration. Although malignant transformation of a dermoid cyst is relatively uncommon, a malignant process in the more complicated teratomas is a fairly frequent finding. Until it has been examined by a pathologist, one does not know what tissue elements comprise the tumor and hence one is unable to predict the chances of malignant transformation. The chief reason for removing an asymptomatic dermoid cyst, however, is the frequency with which it ruptures into the lung,

causing secondary pulmonary complications, rather than the incidence of malignant degeneration.

Dermoid cysts and teratomas of the mediastinum are located anteriorly and usually have their upper border at the level of the lower portion of the clavicle, although it may be in a considerably lower position. A few cases have been repeatedly cited in the literature as examples of dermoid cysts occurring in the posterior mediastinum. Analysis of these few cases indicates that the cysts were bronchiogenic ones incorrectly diagnosed as dermoid cysts many years ago. A teratoma of the retroperitoneal area may, however, extend retropleurally into the lower posterior portion of the mediastinum.

In some cases it is impossible preoperatively to distinguish dermoid cysts and teratomas from anteriorly located bronchiogenic cysts, lymphangiomas and thymic tumors. An intrathoracic goiter can usually be differentiated from a dermoid cyst or teratoma by the higher and more posterior location of the thyroid mass.

SUMMARY

Four cases of dermoid cysts and teratomas of the mediastinum with unusual features are reported. In 1 case there was an intrapulmonary extension of the dermoid cyst. The second patient had a huge teratoma successfully removed at the age of 4 years. The third patient had a bilateral dermoid cyst requiring bilateral operation in stages. The fourth case emphasizes the potential danger of some asymptomatic mediastinal tumors.

ARTHRODESIS OF THE TARSAL BONES

A Study of Failure of Fusions

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SINCE G. G. Davis[1] first demonstrated his procedure for stabilization of the tarsus in 1913, this technic has undergone numerous revisions and refinements until today several modified descendants of the parent operation constitute tested methods for the alleviation of deformities of the foot resulting from many diseases. Operations on the tendons and ligaments, once popular as stabilizing forces in themselves, have now become complementary to fusions of the bones.

The criteria of Hoke[2] formulated over twenty years ago still indicate the aim to be sought. The operation should make the foot appear natural in a shoe, stabilize against lateral forces in standing and walking and supplant braces wherever possible, and it should leave no deformity of the bare foot. Hoke felt that the Davis operation was done blindly, with too scant attention to detail. In this respect he advanced the technic of stabilization of the feet. Since then other outstanding contributions have further refined these technics. The advances made by Hibbs, Dunn, Ryerson, Lambrinudi[3] and Brewster[4] have all been noteworthy.

In this study an effort was made to determine (1) the incidence of bony bridging after fusion, (2) the effect of the underlying disease on the production of osseous union, (3) the types of operations which were most successful in producing bony fusion, (4) the joints which proved most refractory to fusion and (5) the reasons for failure of solid bony union.

Certain operations designed to stabilize the foot done by the Orthopedic Department of the Hospital of the University of Pennsylvania are

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From the Department of Orthopedic Surgery, University of Pennsylvania Hospital.

1. Davis, G. G.: The Treatment of Hollow Foot, Am. J. Orthop. Surg. **11**:231, 1913.

2. Hoke, M.: An Operation for Stabilizing Paralytic Feet, Am. J. Orthop. Surg. **19**:494, 1921.

3. Lambrinudi, C.: New Operation for Drop-Foot, Brit. J. Surg. **15**:193, 1927.

4. Brewster, A. H.: Countersinking the Astragalus in Paralytic Feet, New England J. Med. **209**:71, 1933.

here reviewed. The operations include fusions of several different types, and the data on 53 unselected patients were carefully reviewed and found to be detailed enough for inclusion. More than half of these patients were personally seen. Sixty-five operative procedures were performed for a variety of conditions, the most common being poliomyelitis, cerebral paralysis and congenital deformities of the feet. The follow-up period ranged from one to eight years, with an average of three years.

With some of the earlier developed technics solid bony fusion was regarded as not entirely necessary if clinical (fibrous) fusion resulted, the deformity remained corrected and stability and function improved. Operations on the feet demand a longer follow-up period than many other types of bone surgery as the mechanics of standing and walking are continually subjected to new stresses and strains caused by growth, age and changes in activity, weight, occupation or health. Muscle imbalance, with deformities of the foot may become apparent many years after surgical treatment. In dealing with a procedure so vulnerable to failure and with a condition so subject to insidious recurrence, the surgeon should be content only when the end result is solid bone union.

Accordingly, an extremely rigorous definition of fusion was adopted for the study. All the tarsal bones had to show both clinical and roentgenologic evidence of bony fusion. If two bones were united and the third remained separate, the entire procedure was classified as unsuccessful. The time allowed for fusion to occur was one year (except in 1 instance, in which failure was acknowledged and a revision done after six months). In most instances success or failure could be determined by the third postoperative month. In retrospect, many of the failures could have been anticipated from the appearance of the immediate postoperative roentgenogram. By adopting this standard, it was felt that some light might be cast on this interesting subject.

Of the sixty-five procedures, failure of fusion occurred after fifteen, or 23 per cent. The postoperative follow-up of the 15 patients covered a period of from one to eight years.

No one type of procedure seemed to be more prone to failure than another. This excludes the technics which were used in only a few cases (fig. 1).

An examination of the cases in which union did not occur reveals that operations on patients with infantile paralysis resulted in fewer failures than operations for either cerebral paralysis or club feet. The reason for this is not entirely clear (fig. 2).

The entire series of patients belonged in the established age group for whom fusions are usually required, and there was no significant difference in age between the patients in whom fusion did not occur and those

for whom the operation was more successful. The youngest patient in the group for whom the operation was unsuccessful was 9 and the oldest 22.

Crego and McCarroll[5] have shown that many recurrences of deformity after arthrodesis in children are related to unequalized muscle forces

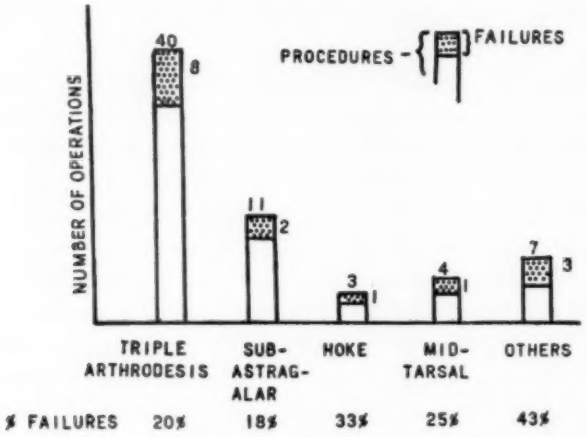

Fig. 1.—Failure of fusion according to various methods.

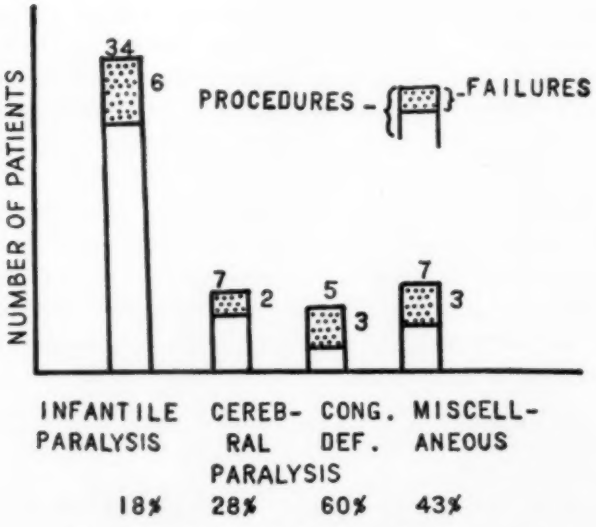

Fig. 2.—Failure of fusion in various diseases.

about the foot. A constant unopposed force in the growing child has a real deforming potentiality. Examination in the cases which failed to

5. Crego, C. H., Jr., and McCarroll, H. R.: Recurrent Deformities in Stabilized Paralytic Feet, J. Bone & Joint Surg. **20**:609, 1938.

demonstrate union in this study showed that in those subject to unequalized forces fusion occurred no less readily than in those not subject to such unopposed forces when the postoperative position of the foot was satisfactory and the lateral pulls carefully controlled in well applied casts. This is understandable because the vital period in the production of a fusion is while the member is enclosed in plaster. When the plaster is removed, the importance of such unopposed forces as causes of deformities in adjacent joints or in those failing to fuse cannot be underestimated.

Some significant facts are revealed when the degree of success or failure in eliminating different joints is studied regardless of the procedure employed, the underlying disease or the age (fig. 3). Practically always the talonavicular joint is the offender. In some instances it re-

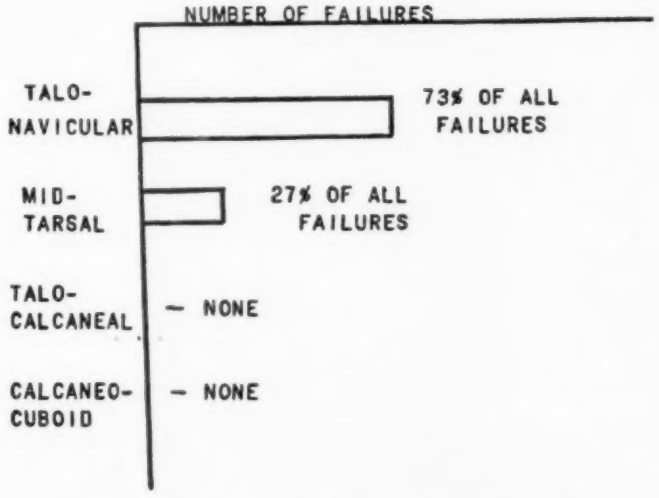

Fig. 3.—Failure of fusion in the various joints.

mained unfused along with the calcaneocuboid, there being a midtarsal hiatus present. Alone, the calcaneocuboid joint was amenable to fusion. In no instance did it remain unfused by itself when an attempt was made to fuse it. The talocalcaneal joint, too, fused readily. Occasionally segments of joint space remained visible in the roentgenogram, but bone fusion of a major portion of the joint invariably occurred.

Of the 14 patients with the fifteen unfused joints, revision was carried out on 3, with subsequent fusion. In 3 of the remaining 11 patients what was regarded as a satisfactory clinical result was obtained. This indicated correction of the deformity, relief of pain and improvement in function. Four of the 8 patients in whom unsatisfactory results were obtained experienced a recurrence of the deformity. Pain and restriction of activity occurred in the other 4.

A careful review of the cases in which fusion did not occur seemed to indicate that there was no one cause for all the failures. In several instances the fore part of the foot was seen to be medially displaced, leaving a large portion of the navicular bone unapposed by the talus (fig. 4). A small lateral segment of the navicular under the best of conditions could have united with the talus. In such circumstances the navicular appendage sclerosed and shrank to a fraction of its original size after

Fig. 4.—Loss of apposition of the talus and navicular joints, with medial displacement of the fore part of the foot.

several years. Often observed was an overhanging navicular bone, with its medial aspect tilted posteriorly. Clinically, it was occasionally possible to palpatate this prominent medial displacement. In such cases the cuboid bone in the anteroposterior roentgenogram was noted to be displaced inwardly also and to be fused to the inner aspect of the os calcis (figs. 5 and 6).

The importance of accurate positioning of the foot in applying the original plaster cannot be overemphasized. Any tendency of the fore part

of the foot to rotate inwardly must be prevented. Particular attention should be given to this detail when unopposed forces are acting. The plaster should be snug. Roentgenograms made through the plaster in the

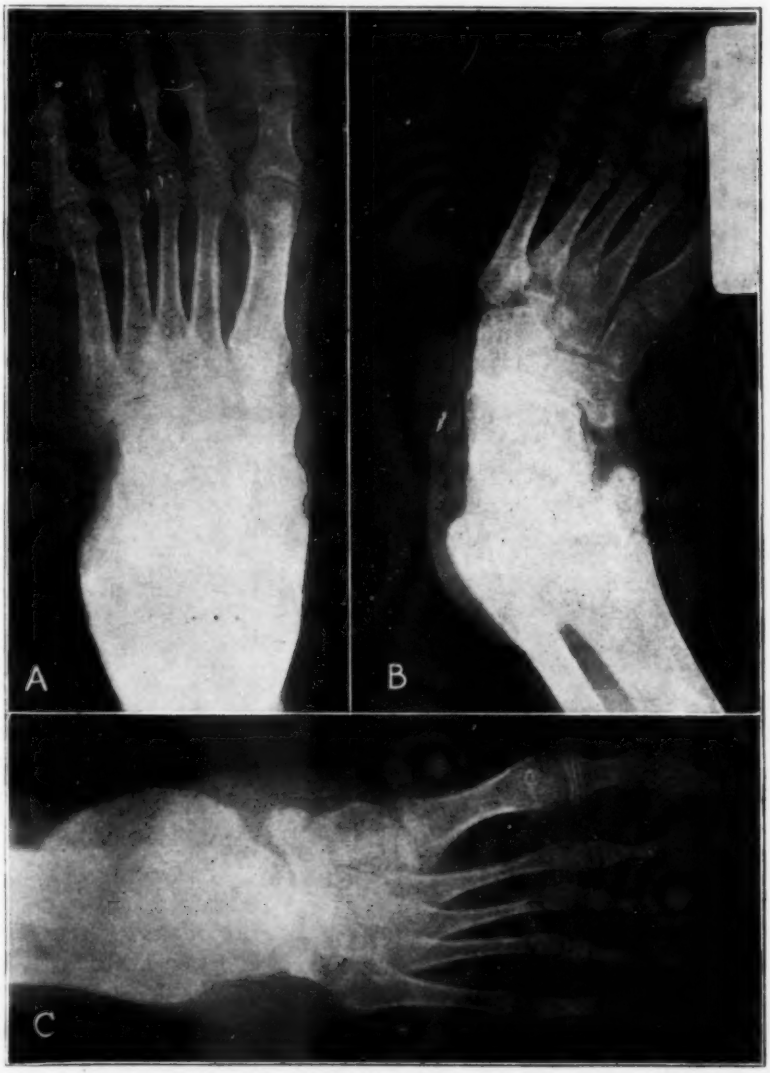

Fig. 5.—*A*, medial displacement of the fore part of the foot; *B*, medial rotation of the navicular joint, with failure of fusion of the talonavicular joint; *C*, medial displacement in a patient with a severe spastic paralysis.

early postoperative period detect deficiencies in position, and correction can be accomplished. In several cases nonunion of the navicular bone could have been anticipated from early postoperative roentgenograms

made through the plaster showing the bone displaced and revealing a complete lack of any semblance of contact with the talus. It is not to be understood that in all the cases in which such displacement was noted the bones failed to fuse. Fusion did occur, but it often required a longer period. The degree of loss of contact appeared to be a decisive factor. Whenever the talonavicular contact is reduced to a minimum, a definite obstacle to success can be forecast.

In other cases there was no definite shift of the fore part of the foot, but the navicular bone itself appeared displaced as an independent entity in a medialward direction (fig. 7). Whether this bone is sufficiently freed from its supporting ligaments after operation to allow it to wander is not known, but it is conceivable that being separated from its attachments

Fig. 6.—Loss of apposition between the talus and navicular bones.

laterally, superiorly, and proximally the anterior fibers of the deltoid ligament and the posterior tibial tendon may exert a levering force. This appearance of a poorly secured bone was most conspicuous when an unduly large amount of bone substance was removed from the navicular and a small interposed fragment partially extruded between the talus and the cuneiform bone. In such instances it was striking to note how the navicular had parted company with the cuboid bone, there being a large gap between the two bones. This is not seen when there is uncomplicated medial displacement of the entire fore part of the foot.

The intact talonavicular joint is of the ball and socket type and relatively stable. Although its configuration is of this type, its motion in the

normal foot is arthrodial because of the many restraining ligaments. In the production of an arthrodesis this relationship is destroyed and two linear surfaces are often substituted for the convexity and the concavity. Thus, the accurate fitting and the stability are impaired, and the joint now becomes more susceptible to lateral forces. In addition, since the talar head is convex and the adjacent navicular surface concave in the intact foot, the effect of destruction of this relationship is to increase the joint surface of the navicular bone and to diminish the joint surface of the

Fig. 7.—Separation of cuboid and navicular bones.

talus, thus producing a disparity. The other joints involved do not undergo such drastic changes in their articular relationships.

A fusion in which the bone contours of the talus and navicular bone remain unchanged may enhance the stability during the postoperative period and allow fusion to occur with a minimum risk of displacement and loss of position. The cartilage of the talus and navicular bone would be removed so as to maintain the necessary convexity and concavity. Sta-

bility stands to be increased, and disparity between the joint surfaces, although still present, will be minimized.

Postoperatively the foot should be placed in position, with meticulous attention given to opposing the hind and fore parts of the foot. Especial care should be employed when strong muscle pull is a factor. Roentgenograms taken after operation through plaster should be inspected, with emphasis on the talonavicular relationship. The long and well established technics for fusion are not intended to be passed over. Complete removal of cartilages and the accurate removal of wedges are of prime importance.

SUMMARY

In arthrodesis the incidence of failure is higher when fusion of the talus and navicular bone is attempted than when other bones are involved. A discussion of possible causes for this is presented. Certain technical features are emphasized and certain concepts offered.

TRIGEMINAL TRACTOTOMY

Observations on Forty-Eight Cases

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AND
INA A. MARSH, M.D.
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IN 1938 Sjöqvist[1] described trigeminal tractotomy, an operation planned to sever the descending spinal tract of the fifth cranial nerve. By this maneuver he was able to relieve patients of facial pain without sacrificing facial touch sensibility. Subsequently others have reported results confirming his conclusions.

Since April 27, 1939, we have performed forty-eight tractotomies, with a 16.6 per cent mortality rate (fig. 1). Thirty-five of the operations were done for the relief of trigeminal neuralgia. The pain involved the first division in 28 cases, was bilateral in 1 and had affected the opposite side after a previous rhizotomy in 6. Two of the 35 patients died, 1 of uremia seven days after operation and 1 after four days of difficult and irregular respiration. Although the operation was attended with no noticeable difficulties, at necropsy the pons and the medulla were edematous, with scattered petechial hemorrhages. This consituted a mortality rate of 5.7 per cent among the "tic" patients.

Thirteen operations were done in conjunction with rhizotomy for the pain due to neoplasms, with 6 deaths in the hospital, a mortality rate of 46 per cent. Three deaths (23 per cent) occurred within a few days of operation, principally from aspiration pneumonia associated with ulcerating masses in the mouth and pharynx.

COURSE IN THE HOSPITAL

Several interesting reactions occurred during the patients' hospital course. Four continued to have pain in the face, for which the wound was

Read before the Society of Neurological Surgeons, Cleveland, June 6, 1947.
From the University of Buffalo School of Medicine and the Buffalo General Hospital.

1. Sjöqvist, O.: Studies in Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, Helsingfors, Mercators Tryckeri, 1938.

opened and the incision deepened; 1 required subsequent rhizotomy. Six exhibited unexplained fever for seven to fourteen days. Two vomited for seven to ten days and 2 had retention of urine for ten days. Five exhibited psychic depression, 2 were disoriented and 1 had hallucinations. These complications cleared before their discharge from the hospital. One patient suffered hysterical quadriplegia which persisted for a year. Herpes occurred, on the upper lip especially, in about 50 per cent of the patients. No corneal ulceration was noted.

FOLLOW-UP STUDIES

In March of 1947 an attempt was made to evaluate the results obtained in the group of 35 patients operated on for trigeminal neuralgia

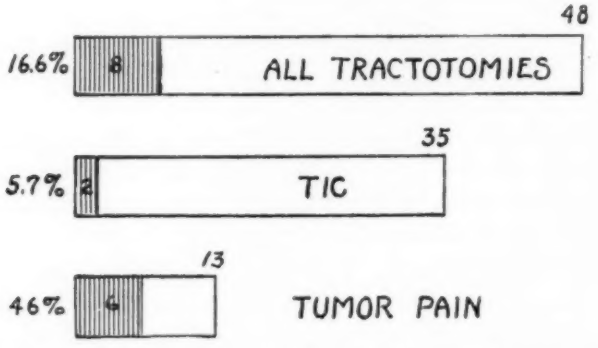

Fig. 1.—Surgical mortality (shaded) in 48 cases of tractotomy.

(fig. 2). Of the 33 survivors, 25 were examined, 3 responded by letter and 5 could not be traced.

Ataxia.—Since Sjöqvist's original report, ataxia of the ipsilateral arm has been the most commonly described neurologic complication of tractotomy. Grant and Weinberger[2] found on anatomic study that the restiform body and the main or lateral cuneate nuclei are vulnerable at the level of section suggested by Sjöqvist, i.e., at the lowest vagal rootlet. This level itself is variable, being between 12 and 8 mm. above the obex of the fourth ventricle. Grant found that at a level 4 to 5 mm. below the obex the restiform body is not present and the trigeminal tract is covered only by the external arcuate and the dorsal spinocerebellar fibers. He stated that incision here could not injure the restiform body or the cuneate nuclei and at a depth of 3 to 4 mm. will encompass all fibers of the trigeminal tract, assuring adequate facial analgesia.

2. Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: IV. Surgery of the Brain Stem and Its Operative Complications, Surg., Gynec. & Obst. **72**:747-754 (April) 1941.

In the attempt to avoid ataxia, we have followed Grant's lead in shifting the level of incision. In the first 5 patients the section was made at the level of the lowest vagal rootlet. Only 1 of these patients was examined; he had no ataxia. Section was made at the level of the obex in 4 patients; 3 of these have ataxia of the arm, 2 of severe degree. Section was made 4 mm. below the obex in 5 patients; of 4 of these who were examined, 1 has slight ataxia of the arm. In 21 patients the section was made 10 mm. below the obex; 15 of these were examined, and 4 display minimal ataxia of the arm.

Pain.—Ten of the 28 patients have been free of pain since operation, 5 have noticed occasional fleeting pains in the face, 6 have suffered typical but bearable neuralgic pain and 7 (21 per cent) have suffered typical

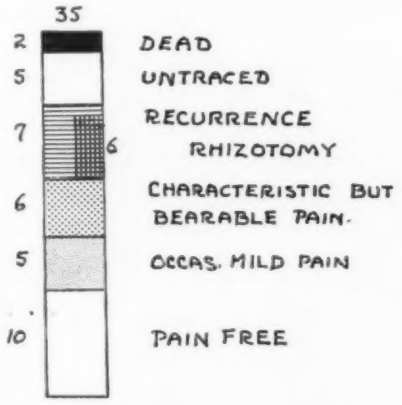

Fig. 2.—Results of tractotomy in 35 patients with trigeminal neuralgia.

recurrence of "tic" pain. Sensory rhizotomy has been performed on 6 of these.

Dysesthesias.—Dysesthesias of the face were experienced by 12 of the 28 patients (43 per cent); 7 of these had residual pain, and 5 were without pain. These sensations were described as "uneasy," "cold," "tickling," "itching," "stinging" and "swelling" and in 2 cases as "painless" or "phantom" tic. In none of the 12 patients did they have the obsessive quality sometimes observed after trigeminal rhizotomy.

Residual Sensation.—Tractotomy produces analgesia and hypothermesthesia of the trigeminal distribution area, leaving touch sensation relatively intact. As have practically all other writers on the subject, we found the ophthalmic division the most uniformly denervated and the mandibular division the least. The level of section apparently did not make much difference in this distribution, but depth of section did. In 3 cases faulty analgesia was improved by reoperation, in which the section was deepened

at the same level. Grant, Groff and Lewy[3] noted that in cross section of the medulla the descending root appears as a crescent, with the tongue and lip represented at the superior-median tip, the third division dorsally, the first division at the ventrolateral tip and the second division occupying the mid-portion. They stated that failure to relieve pain in the tongue and lip can be avoided by correct placement of the incision. This requires careful attention to the dorsomedian angle, care being taken to avoid the cuneate tract.

Twenty-two of the patients examined had undergone tractotomy only, without rhizotomy. Twelve (54 per cent) of these displayed in their analgesic zones patches of normal or near normal sensation (fig. 3*B*). In 4 patients these areas reacted as "trigger zones" when rubbed. The pain-sensible areas usually were small, though in 1 patient practically

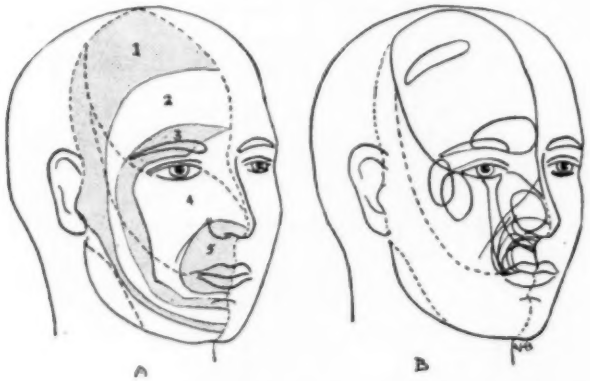

Fig. 3.—*A*, "onion skin" pattern of areas according to Dejerine. *B*, superimposition of patterns of retention of pain perception in 12 patients.

the entire first division remained sensitive, as in a case reported by Grant, Groff and Lewy. In 8 cases the pain-sensible areas were on the upper lip and on the side of the nose. In 2 cases they were at the outer edge of the orbit, in 1 above the brow and in 1 at the hairline lateral frontal area. Grant and his co-workers found pain sensibility of the tongue spared in 4 and that of the lip spared in 3 of 12 patients reported in 1940. They remarked that it was questionable if the pain of trigeminal neuralgia would have been relieved had it originated in these areas.

The older neurologic and neuroanatomic texts described an "onion skin" distribution of zones of the face (fig. 3*A*), attributed by Dejerine to the morphologic arrangement of fibers in the brain stem. This descrip-

3. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:498-509 (March) 1940.

tion is rarely seen in a modern text. Kreig described it in his "Functional Neuroanatomy" in 1942. In a review of the book appeared the notation: "The old 'onion skin' distribution of sensation of the face presumed to result from the distribution of the sensory fibers in the brain stem, shown in Fig. 134b, is not in accord with recent clinical observations." Grant, Groff and Lewy found that in 1 of their patients "analgesia was complete in division I only and partial in the second and third, with an 'onion skin' hypalgesia around the upper lip and mouth, similar to that which has been described in cases of bulbar lesions of the nucleus of the fifth cranial nerve." Superimposition of patterns of residual sensation found in our patients produces a picture (fig. 3*B*) which tends to lend support to the idea of some such arrangement. At least, it may be safely said that the fibers supplying the region of the tongue, upper lip and side of the nose have been the least vulnerable to attack in this series.

Corneal Reflex.—Sjöqvist noted that touch sensation was retained in the cornea after tractotomy although the patient did not feel pain. Rowbotham,[5] Grant and his co-workers, Brodal[6] and others have made similar reports. Probably because nerve endings believed to initiate pain impulses only have been found in the cornea, neurologists have been reluctant to accept the idea of the persistence of corneal reflexes. Regularly, however, it is found that touch is perceived in the cornea, and in most cases this is sufficient to elicit a wink reflex. This is of diminished force but appears to be a true corneal reflex. We do not believe that this should be designated as "absence" of corneal reflex with any more reason than one would have for describing as "absent" an ankle jerk which can be elicited only with reenforcement.

Sensation in Other Cranial Nerve Areas.—In March 1947 Brodal of Oslo reported the sensory changes found in 4 patients after tractotomy performed by Dr. Torkildsen. In addition to analgesia and retained tactile sensibility in the trigeminal area of the face and mouth, he found similar changes in other areas. These included the concha of the auricle, with more or less of the neighboring part of the antihelix, the posterior third of the tongue and the part of the tonsil and pharynx on the side operated on. In 1 case also a small area behind the ear was included, and in 2 cases the analgesia extended to the posterior, upper and anterior

4. Krieg, W. J. S.: Functional Neuroanatomy, Philadelphia, The Blakiston Company, 1942, p. 553; reviewed, J. A. M. A. **119**:849-850 (July 4) 1942.

5. Rowbotham, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, Brit. M. J. **2**:1073 (Nov. 26) 1938.

6. Brodal, A.: Central Course of Afferent Fibers for Pain in Fascial, Glossopharyngeal and Vagus Nerves: Clinical Observations, Arch. Neurol. & Psychiat. **57**:292-307 (March) 1947.

walls of the external auditory meatus. From these observations he concluded that fibers conducting pain impulses in the facialis-intermedius complex, the glossopharyngeus and the vagus join the pain fibers of the trigeminus and accompany them in the descending spinal tract of the trigeminal nerve. He suggested that neuralgias of these nerves, as well as those of the fifth nerve, may be successfully treated by tractotomy.

This report appeared subsequent to the examination of our patients, so the sensitivity of these areas was not studied. Five patients have been recalled and these areas reexamined specifically. Three of these were of the group who had complete facial analgesia without recurrence of pain. They were found to have analgesia of the entire ipsilateral half of the tongue, palate, uvula and tonsil and its pillars and of the accessible portion of the pharynx. All 3 had analgesia of the entire auricle and external meatus and of an area behind the ear extending down on the mastoid process. Two of the patients were among those readmitted to the hospital for trigeminal rhizotomy because of recurrence of facial pain. They had persistence of pain perception in the upper lip and the nose, which indicated an incomplete section of the trigeminal tract. Both of them retained most of their pain perception in the tongue, palate, fauces and pharynx. Analgesia extended irregularly over and behind the ear.

The level of section in the medulla was not the determining factor in our cases. In Brodal's cases the incisions were described variously as being made "according to the method of Sjöqvist," 2 mm. rostral to the caudal end of the fourth ventricle, at the inferior end of the fourth ventricle and "according to the same principles as those observed with the other patients." In general, the level of section appeared to be at or above the obex of the fourth ventricle. In our 5 cases the sections were made 10 mm. below the obex in 4 and at the level of the lowest vagal fiber in 1.

It would appear that our findings agree generally with those of Brodal. Because of the impression of the poor reliability as witnesses of our small group of 5 patients and the failure of the analgesic zones over the ear to follow anatomic lines, we are unwilling at present to offer these data in evidence supporting Brodal's conclusions concerning the course of the pain fibers of the seventh, ninth and tenth nerves. The surgical applicability of these conclusions demands findings based on a larger and more reliable group of patients.

SUMMARY

Report is made of the performance of forty-eight trigeminal tractotomies, with a 16.6 per cent mortality rate. Thirty-five operations were for trigeminal neuralgia, with a 5.7 per cent mortality rate. Thirteen operations were for pain due to neoplasms, with a 46 per cent mortality rate.

Follow-up studies were made on 28 of the 33 survivors in the group with trigeminal neuralgia; 25 were examined, and 3 responded by letter. Ten patients are free from pain, 5 have had occasional mild pain and 6 have bearable recurrence of neuralgic pain. Seven (21 per cent) have suffered typical recurrences of pain, 6 of whom required rhizotomy.

Ataxia of the arm was found in 8 of 24 patients examined.

Mild facial dysesthesias have been experienced by 43 per cent of the patients.

Residual sensation in 54 per cent of the patients persisted chiefly in the lip and in the side of the nose, resembling incomplete "onion skin" patterns.

In 3 patients with complete trigeminal analgesia, the zone also includes the auricle, an area behind it, the entire half of the tongue, palate and tonsil and the accessible part of the pharynx. In 2 others with incomplete facial analgesia irregular analgesia extends into the sensory domain of the seventh, ninth and tenth nerves.

Surgical Clinics

SURGICAL CLINICAL CONFERENCE ON DISEASE OF THE GALLBLADDER

SURGICAL STAFF, PASSAVANT MEMORIAL HOSPITAL
CHICAGO

The biweekly surgical conference at the Passavant Memorial Hospital, a teaching unit of Northwestern University Medical School, Chicago, was held at 12 o'clock on March 18, 1948.

DR. FRANK LOUNSBURY: Today, we have an interesting clinical problem. It is interesting because it presents not only a problem in diagnosis but also a question in the matter of treatment.

Dr. William Daines was the first person to see the patient after she was admitted to the hospital, so I will have him present the case.

DR. WILLIAM DAINES: The patient, Mrs. A. F., a 63 year old woman of German descent was admitted to this hospital about noon on Feb. 24, 1948, with complaints of moderately severe pain in the upper abdominal area, nausea and vomiting of about twelve hours' duration.

Her past history revealed numerous abdominal operations—an appendectomy in 1917 and an ovarian resection and a uterine suspension. In 1945 she had an attack of jaundice, and a cholecystostomy, with removal of stones, was performed; relief of the jaundice followed. The following year she underwent a cholecystectomy. Shortly after this operation she had an episode of rather severe pain in the upper abdominal area, nausea and vomiting which lasted for about two days apparently without any evidence of jaundice.

A similar episode occurred six months later, which lasted two days and disappeared without medication.

In December 1947 she was admitted to this hospital for the first time. A hysterectomy was done for postmenopausal bleeding. At the time of the operation an attempt was made to explore the gallbladder area, but it could not be reached because of numerous adhesions. A few days after she had an evisceration and was taken to the operating room, where repair was carried out. She had a stormy course for a few days, but she recovered and left the hospital in good condition.

She was well until twelve hours before her admission in February 1948. About 10 o'clock on the night preceding her admission she had a rather acute onset of nausea and vomiting and pain in the upper abdominal area. The pain was felt across the upper part of the abdomen and radiated back to both costovertebral angles. The patient seemed to think the pain was constant. However, the daughter, who was with her all the time, said she had exacerbations. She would complain bitterly, be relieved for a while and then complain again. So we were not certain whether the pain was constant.

The pain persisted, and the patient had numerous emeses and was nauseated all night. The next day she entered the emergency room shortly before noon. She had had a normal bowel movement the night before and one the morning before admission.

On examination, she was found to be obese. She was in moderately acute distress. Her temperature was 100 F. and the blood pressure 180 systolic and

100 diastolic. Her tongue was dry and her skin warm and dry; the lungs were resonant throughout. She was unable to take a deep breath because it produced more pain. A few moist rales were heard in the lower part of the left lung. Her heart was enlarged to the left, the tones were distinct and there were no murmurs. The abdomen was obese but not distended, and there was no rigidity. Bowel sounds were present throughout the abdomen and were quiet. Tenderness was present over the entire epigastrium and was more prominent to the right of the midline. There was no rebound tenderness. The liver and the kidneys were not palpable. There was moderate tenderness bilaterally in the costovertebral angles.

Laboratory study revealed a white blood cell count of 25,000. The urine was normal except for 15 red cells and 10 to 15 white cells per high power field.

The blood amylase content, determined shortly after her admission, was 383 mg. Shortly after the onset of pain, the dextrose index was 16. The electrocardiogram showed left axis deviation without any other diagnostic deformities. A scout roentgenogram of the abdomen was essentially normal, with no signs of any obstruction of the bowel and no sign of a gallstone or a renal or urethral stone.

Surgical consultation was obtained shortly after admission, and it was decided that conservative management should be followed. The patient was given fluids and started on penicillin. Her condition became steadily worse throughout the night. She had a chill in the morning, with a temperature of 106 F. The respirations became more rapid and more shallow. She became semicomatose in the afternoon, and about 7:30 in the evening she went into shock. Treatment was without result, and she remained in shock for about twelve hours. The urinary output decreased markedly, and about 8 o'clock the next morning she died.

DR. LOUNSBURY: We will ask Dr. Walter Nadler to discuss the diagnostic possibilities which should have been entertained and the treatment.

DR. NADLER: I happened to see this patient in the examining room while she was awaiting a hospital bed. It was obvious that she was extremely ill. At that time I did not know the complete history.

It seemed to me that the problem was one of diagnosis, with particular regard to a therapeutic approach, whether medical or surgical. She had had extreme pain, nausea and vomiting. With regard to the history of two operations on the gallbladder, information as to the surgical procedures employed would have been of value. It was stated that when the later hysterectomy was performed multiple adhesions were present and that this made it impossible to explore the upper part of the abdomen.

The patient entered the hospital with the complaint of pain which was rather continuous although varying in intensity. She had fever, had been vomiting and was dehydrated and in a state of acidosis. There was slight generalized distention of the abdomen.

I believe that Dr. Daines, as an internist, properly called a surgeon at once to see the patient. It seemed to us that this was a surgical case. The only other possibility was that an acute virus hepatitis was present, although this would not begin with such pain as was decribed.

As far as possible in conditions requiring surgical treatment one would have to consider an obstruction of the bowel or a perforation. However, on the basis of experience with similar cases, one would consider most strongly the diagnosis of a stone in the common duct, with associated cholangitis or pancreatitis. Several years ago we had a patient with the latter condition, and we waited much too long; the patient died of shock due to pancreatitis.

On the assumption that the pathologic process present required surgical intervention, the next question was whether the approach to surgery could be deliberate, with preparation of the patient, or whether an emergency existed for which prompt surgical intervention was necessary in order to save the patient's life. Opinions in that regard were, it seems, tossed back and forth. Perhaps we were not emphatic enough in our own point of view in that respect. It seems to me that the patient needed immediate surgical treatment, regardless of all the risks that were entailed. The measures, ordinarily desirable, intended to prepare this patient for operation were, as it turned out, futile. She failed to revive sufficiently to reach a state in which operation would seem safe. It was my opinion and Dr. Daines', I believe, that she had a gallstone in the common duct and that she probably had an associated pancreatitis.

DR. LOUNSBURY: Thank you, Dr. Nadler. Dr. Walter Maddock, do you care to discuss this case?

DR. MADDOCK: This case appears to illustrate the higher mortality rate that goes with disease of the gallbladder in older patients. In almost all series of cases the mortality rate is relatively low when the patients are under 50 years of age and is higher for patients over 50 because of (1) other diseases such as obesity and hypertension, which this patient had, (2) previous operations, with complications like evisceration which keep the patients from undergoing surgical treatment, and (3) the complications of long-standing disease of the gallbladder, i. e., hepatitis, cholangitis, choledocholithiasis and pancreatitis.

Just as Dr. Nadler has mentioned, one would like to know whether there had been exploration of the common duct at the time of the second operation because the presence of jaundice at the first operation and of continued symptoms makes one suspect a stone in the common duct. It may have been proper at the first operation on the gallbladder simply to have drained the gallbladder and to have done nothing further. But when the gallbladder was taken out in 1946, information should have been obtained as to the condition of the common duct at that time, viz., whether it was dilated, whether the wall was thickened or there were other evidences of inflammation such as large lymph nodes and certainly whether there were stones in the common duct. The condition of the head of the pancreas would also be important.

From the history of recurrent pain after the operations, the diagnosis of a stone in the common duct is probably the most correct one. The next possibility is the presence of a second complication which is associated with disease of the gallbladder, i. e., pancreatitis.

The patient was admitted to the hospital in exceedingly poor condition. The leukocyte count of 25,000 is a high one. I was taught a long time ago that one could be conservative in dealing with disease of the gallbladder as long as the count was under 25,000 but that after it had reached 25,000 one should think of gangrene of the gallbladder wall, with cholangitis and hepatitis and other complications, and that operative treatment then is indicated. However, this patient was not in good enough condition at the time of admission for such treatment.

DR. LOUNSBURY: I think the others who are going to comment on the case saw the patient during the subsequent course, so this information is not new to them. Dr. Douglass, do you care to discuss the case?

DR. THOMAS DOUGLASS: I saw the patient after the second day of her stay in the hospital. At that time she was in no condition for any type of surgical treatment.

However, I think there are a number of interesting things about the patient and that there are many things which we can learn from this case.

I should like to second the comments which Dr. Maddock made about the operations in 1945 and 1946 and to raise a question. Was the gallbladder actually removed in 1946? I should also like to ask a question about the hysterectomy. Did the two attacks occur between the cholecystostomy and the hysterectomy? If so, why was a hysterectomy performed instead of further exploration of the biliary tracts in 1947? It seems to me that on account of the story of the attacks, even though she had no jaundice, one might have been suspicious then of further pathologic changes in the biliary tract. Of course, this brings out the fact that the ducts should have been properly explored at the time of the operation in 1946 if not in 1945.

The study of cases which Dr. Lounsbury and I made here at this hospital confirms the statements which Dr. Maddock made concerning the mortality rate in the older age group. Twenty-five per cent of the deaths after cholecystectomy were in the older age group, whereas only 7 to 10 per cent of the patients were in that age group.

There is another question which is interesting to me: Why did she die? We have seen many cases in which disease of the gallbladder with repeated attacks and even with stones in the common duct subsided, even though the patients were seriously ill. What was different about this woman? Other patients who have had many attacks apparently as severe, clinically at least, have been made ready for operation in a period of a few days or a few weeks.

I do not think that we have any clue in the history of this case, but there may be a clue. In the subsequent discussion by the pathologist I should like to have him tell us if the marked fatty degeneration in the liver had anything to do with the reticuloendothelial system in preventing it from being active and helping the patient to overcome a serious infection. Why were the changes present so much more profound than the usual changes which occur in the liver with repeated attack of gallbladder disease? When I saw the woman, I thought that pancreatitis was more likely to be the cause of the sepsis than cholangitis.

We might learn something more about the liver in operations on the gallbladder after careful preoperative preparation if more histologic study of material from the liver were carried out. Some of the liver function tests could then be correlated more closely with the pathologic changes as shown by the biopsy.

I certainly could offer no criticism whatever of the management of this patient after she was admitted to the hospital, because when I saw her she could not have tolerated surgical intervention. The time for that was after her previous attacks.

DR. LOUNSBURY: In answer to Dr. Douglass' question as to why the hysterectomy was done instead of further exploration of the biliary tract, I think that it was performed on the gynecologic service for postmenopausal bleeding, which was presumed to be due to a carcinoma of the uterus. An attempt was made to explore the upper part of the abdomen, which was unsuccessful because of the numerous adhesions.

Dr. Hoebel, you saw this patient. Would you care to discuss the case?

DR. FREDERICK HOEBEL: I saw the patient shortly after her admission to the hospital, and I followed her progress. She presumably was subjected to cholecystostomy, followed by cholecystectomy. I say presumably she had a cholecystectomy. She

had been told that the gallbladder had been removed, but if it was not removed then it is fair to assume that the common duct was not explored.

I feel that the principal problem in this case was not diagnosis. We made an initial diagnosis in the emergency room of stone in the common duct with obstruction. The written diagnosis on the chart was stone in the common duct, with obstruction, cholangitis and possible pancreatitis.

The problem, then, was one of judgment, and the previous training which I have received in this school has been entirely toward conservative treatment in these cases. This attitude is based on the fact that when there is obstruction of the common duct by stone the latter will dislodge in most instances and drainage will be reestablished. The problem is to discover in which case drainage is not going to be reestablished when the stone is in the duct.

It seems to me that in a case of this sort we may be violating surgical principles if we do not drain the common duct. I feel that if we carry a patient on for a number of days or even weeks who has repeated obstructions or constant partial obstruction of the common duct with cholangitis, we are violating these principles. First, we are allowing obstruction of the duct on draining an organ, with resultant damage to the cells of that organ. Secondly, we were failing to establish drainage of the area of cholangitis, which is analogous in many respects to failure to drain an abscess.

In this case we were defeated by the fact that the patient deteriorated rapidly, much more so than we had anticipated and more so than I have ever seen a patient deteriorate in the past. She came into the hospital late in the afternoon, and the following noon her condition was too poor for any surgical treatment at all. Had we operated the day that she came in, we might possibly have accomplished something. Perhaps we would have been defeated at that time, too. I think that our conservatism was established at a time when operations and anesthesia carried considerably more risk than they do now, and I wonder if we should revaluate our judgment.

I know that there are others who feel that early or relatively early surgical intervention, with simple drainage of the common duct, is indicated in these cases.

DR. LOUNSBURY: Thank you, Dr. Hoebel. Before we have any other comments, perhaps we should round out the picture by having someone from the pathology department describe the postmortem findings. Dr. Wheelock!

DR. MARK WHEELOCK: The diagnosis was substantiated by the findings at autopsy. There was a stone in the common duct. There were both acute and chronic cholangitis, notable icterus and dilatation of the common and hepatic ducts and of the pancreatic duct. In addition, there were a hypertrophied heart, atelectasis of the lungs, pronounced obesity and disease in the kidneys. The gallbladder had not been removed previously.

I have quickly noted here the number of anatomic factors in opposition to a successful operation. They are icterus, hypertension, obesity, sepsis, atelectasis and, in addition, a history of previous wound disruptions.

There was septicemia due to Streptococcus gamma, the organism grown in the postmortem blood culture.

There was enough chronic inflammation in the pancreas to indicate its presence for some time. In answer to Dr. Douglass' question, there was extensive fatty degeneration in the liver, a change now accepted as a factor in reducing a person's ability to ward off an infection.

DR. LOUNSBURY: Thank you, Dr. Wheelock. Are there any other surgeons or internists who have seen the patient and who would like to comment on the case?

DR. MADDOCK: I should like to say something further. It is true that at least in one of the two operations on the gallbladder adequate or proper surgical treatment was not given, and this patient ultimately died from disease of the gallbladder and its complications because of that fact. The number of cases in which one has to carry out drainage of the gallbladder is now often well under 10 per cent of any series, because the symptoms and signs of a gallbladder attack subside in most instances, particularly when the patients are younger and have good management. A cholecystostomy is indicated when the patient has considerable evidence of infection or is elderly; then the simplest procedure is the one of choice.

This patient had sufficient evidence of obstruction of the common duct early in the course of her disease to warrant a choledochostomy. Before operation, one can be of the opinion that the common duct in any particular case should be explored because of the finding of jaundice or a history of jaundice in the course of the disease or of a history of clay-colored stools. The latter is not an absolute indication because the diet can result in light stools, but one must think of obstruction of the common duct when clay-colored stools are present. Chills and fevers during the course of the disease are important and generally mean a severe infection and often cholangitis and hepatitis. Then, during the course of the operation, one finds conditions which call for an opening of the common duct; e g., a mass of small stones in the gallbladder is important, for small stones can get down through the cystic duct into the common duct and cause occlusion. This does not occur so often when there are large stones in the gallbladder. The finding of a dilated common duct, a thick-walled common duct, a stone or a questionable mass in the common duct or a suspicious mass in the head of the pancreas calls for an opening of the duct and an exploration.

The mortality is a bit higher when one opens the common duct, possibly by 1 or 2 per cent, but this is considered to be due not so much to the opening of the common duct as to complications that go along with the need for opening it, such as cholangitis and hepatitis. This patient had some good reasons for having her common duct explored originally.

Another point here is the question of whether we could have found out more about the previous operations on the gallbladder. Was this patient operated on locally, and could we have gotten a proper operative report?

DR. DAINES: She was not operated on in Chicago in 1945 or 1946.

DR. MADDOCK: Sometimes I think that we miss the opportunity of learning more about a patient by failing to ask another hospital for the previous operative report.

It is not uncommon to find remnants of a gallbladder left after a so-called cholecystectomy. It used to be an acceptable procedure to leave a small amount of the gallbladder in place when there was pronounced edema about the common duct or about the lower end of the gallbladder. Few good surgeons will now leave a remnant of the gallbladder, because the remnant often enlarges and all the symptoms and signs of cholecystitis may recur, just as they did in this case.

One of the objections that has been raised to the early or immediate surgical treatment of cholecystitis, that is, operation in the first twenty-four or forty-eight hours after the symptoms start, is that considerable edema may be present around the common duct and it is more difficult to visualize this duct or the cystic duct or artery. Exploration of the common duct is not so easy in the early procedure.

DR. LOUNSBURY: Dr. Nadler raises the question of how much of the gallbladder was left. Dr. Wheelock?

DR. WHEELOCK: The major part of the gallbladder was dissected at necropsy.

DR. NADLER: Were there stones?

DR. WHEELOCK: There were no stones in the gallbladder. There were prominent fibrous adhesions around it due to previous operations.

DR. HOEBEL: There is one point which might come up again, and that is: Since this patient received penicillin, how valuable is it to such patients? It is of practically no value, and neither is streptomycin of any value, as long as the duct is undrained. That has been proved experimentally by checking the concentration of penicillin and streptomycin in obstructed and unobstructed common ducts. It has been borne out by clinical experience that it is of little value unless drainage is established.

DR. MADDOCK: What were the causes of the death of this patient?

DR. WHEELOCK: The septicemia is the important factor. Certainly there was not sufficient evidence of pancreatic involvement. There was no cardiac failure despite the fact that she had hypertension and an enlarged heart, which would leave me with one final conclusion, namely, that the infection was the primary cause of death.

DR. MADDOCK: Would that account for the shock shown by this patient?

DR. WHEELOCK: I think so.

DR. MADDOCK: This patient had shock before she died?

DR. WHEELOCK: Yes, the terminal blood pressure was 80 systolic and 60 diastolic.

DR. NADLER: I think we forget that there is such a thing as shock in severe acute infections, whereas shock from injuries and burns is well understood. Years ago, Dr. Keeton, studying a group of patients at the Cook County Hospital during an influenza epidemic, called attention to the importance in treatment of recognizing the presence of shock.

In this case, I believe that shock was due to previous predisposing renal damage and acute sepsis and was aggravated by the dehydration which followed.

From a medical standpoint, I think the moral in this case is that if all patients with gallstones were operated on early enough, before they had to undergo cholecystostomy instead of cholecystectomy, results would be more favorable. I also think, as Dr. Hoebel said, that there should perhaps be a review of our position in regard to a prolonged preparation for operation on all patients with disease of the gallbladder. I am sure that in many instances we wait much too long, since we have available now blood transfusions, streptomycin and penicillin, vitamin K and other accessory food factors. The patients can often be prepared for surgical treatment in a matter of days, whereas we have often waited for many weeks.